The American Journal of Medicine

October 1950

The American Journal of Medicine

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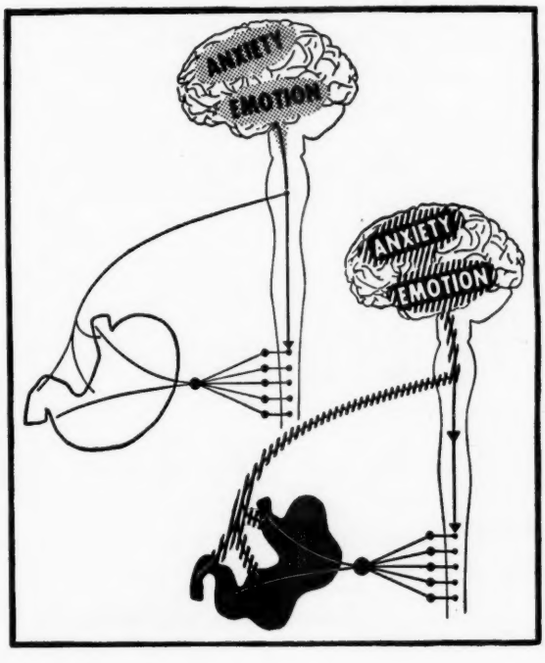
". . . about 50% of the patients who consult the general practitioner have complaints for which there is no discoverable physical or organic cause."[1]

Emotional response and adaptation to stress of the times play major roles in the increase of functional disorders. Exaggerated emotional response may produce somatic symptoms such as vague pains referred to various organs. Nausea, headache, cardiac and gastrointestinal distress are often presenting complaints. Diagnosis is usually easy in these cases because the number and variety of symptoms are not corroborated by physical findings. *Yet, these patients are seriously ill and merit attention and relief. Recent research has indicated that functional disturbances may develop into organic disease if long continued*[2]. In functional disorders, response to stress is effected via both branches of the autonomic nervous system. Therefore, treatment consists, where possible, in removal of the emotogenic factor (practical psychotherapy) and the "partial blockade" of the efferent autonomic pathways.

The family physician is well qualified to help these patients since he is most often aware of the environmental circumstances. His advice and guidance will do much to achieve the desired change in activities and habits and will help the patient to avoid "unhealthy situations".



Medical treatment is also essential in most cases. Controlled sedation of the entire autonomic nervous system accelerates recovery. This is accomplished by simultaneous administration of Bellafoline (cholinergic inhibitor), ergotamine tartrate (adrenergic inhibitor) and phenobarbital (central sedative).

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Brochures available on request:
"The A.N.S. and Functional Disorders."
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*Guerriero, W.F.: *Texas State Jour. Med.*, 45:274, May, 1949.

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CONTENTS

The American Journal of Medicine

VOL. IX OCTOBER, 1950 No. 4

Editorial

Clinical Studies

The first of these two papers records the effects of hospitalization *per se* in eighty-six patients with essential hypertension when maintained on a regular diet for a protracted period. The data on changes in symptomatology, basal blood pressure, heart size, electrocardiographic findings and retinopathy afford a baseline for the data in the second paper which deals with the effects of the unmodified Kempner rice regimen in fifty hospitalized hypertensive patients. The results obtained with the rice diet are in essential agreement with those described by Kempner. However, as a means of sustained treatment of severe essential hypertension the unmodified rice regimen was found to be so difficult for both patient and doctor to maintain that the authors consider it to be impracticable for general use. Preliminary efforts to diversify the diet so as to make it more generally available are described.

The data indicate a significant fall in total, free and esterified serum cholesterol in a large group of hypertensives on the rice diet.

This is a detailed and informative analysis of the results of thoracolumbar sympathectomy performed over a six-year period, 1942 to 1948, in 500 patients. Statistics on survival rates indicate definite prolongation of life in advanced cases (group IV) of hypertension.

Contents continued on page 5

according to therapeutic plan... HYDROCHOLERESIS

In biliary tract disorders, present-day medical management hinges on stimulation therapy and non-surgical drainage. A therapeutic plan is to flush and drain the hepatobiliary tract by *increasing the volume of bile while reducing its viscosity,* solid content and specific gravity.

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CONTENTS

The American Journal of Medicine

VOL. IX OCTOBER, 1950 NO. 4

Contents continued from page 3

FORENSIC MEDICINE

Carefully considering the needs of the general practitioner, Dr. Kerr has written this illuminating book on the reliable action to be taken in cases of medico-legal problems.

He fully discusses the subject of identification, changes after death and various types of murder. Many photographs of cases occurring in his own practice have been included. The practitioner and student will find informative sections on the effects of heat, cold, starvation and neglect.

Primarily Dr. Kerr discusses those legal problems which are relative to the medical practitioner. Heretofore the practitioner has found himself sorely in need of this knowledge, but never before has it been presented with such clarity, completeness and interest.

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THE PRODUCTION OF ANTIBODIES

Based on the presently adopted approach that antibody production is a biological rather than a chemical phenomenon, this is a review of current knowledge and theory as well as a discussion of the authors' research findings since the publication of the first edition in 1941. It is entirely concerned with the evidence bearing on the processes of antibody formation and an attempt to interpret these findings in biological rather than chemical terms.

The authors discuss the function of plasma proteins briefly, then proceed to develop their theory, the "self-marker" concept, by consideration of variations in concentrations of antibody in the blood of immunized animals, qualitative differences amongst antibody molecules, sites of and possible continuity of production of antibodies, and the immunological behavior of young animals.

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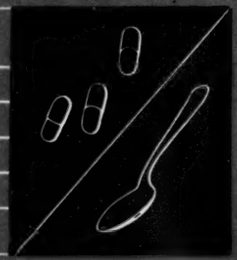

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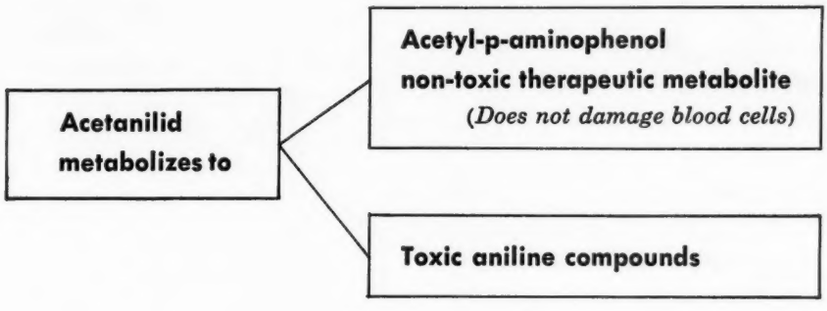

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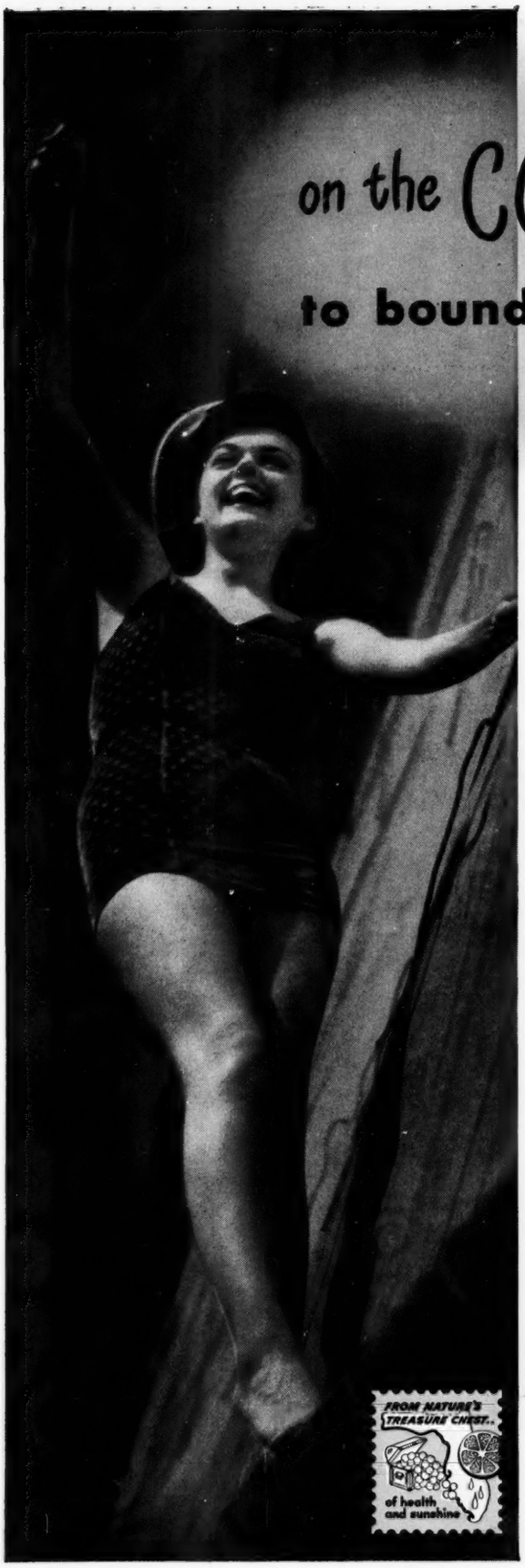

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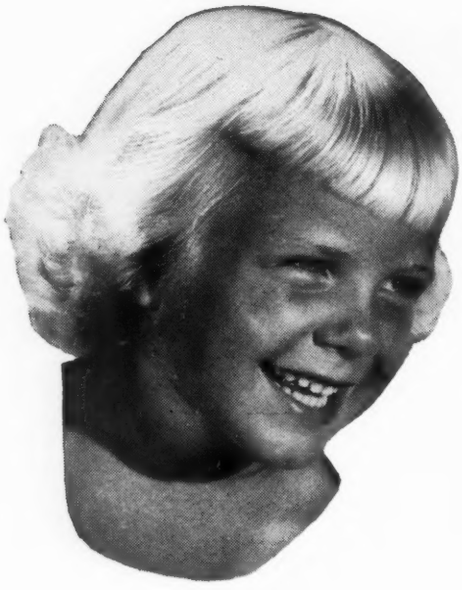

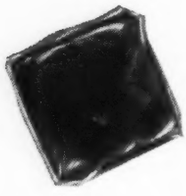

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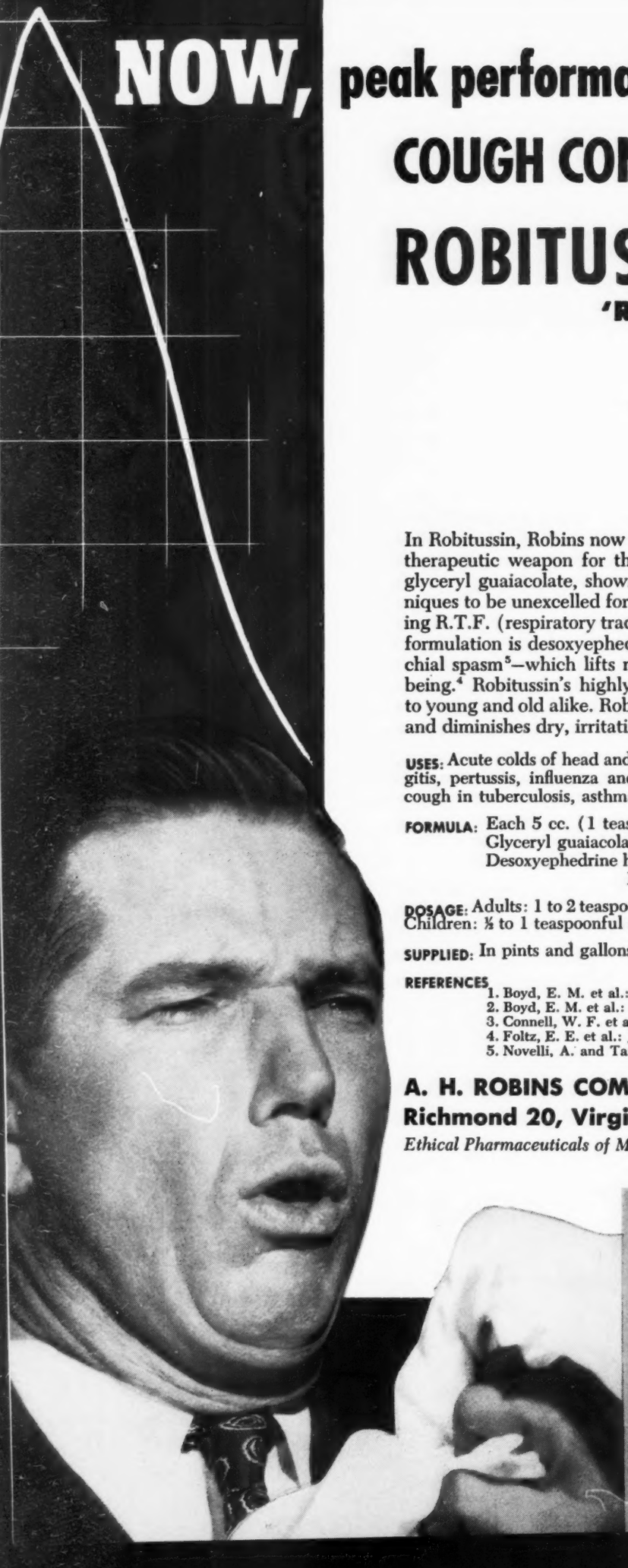

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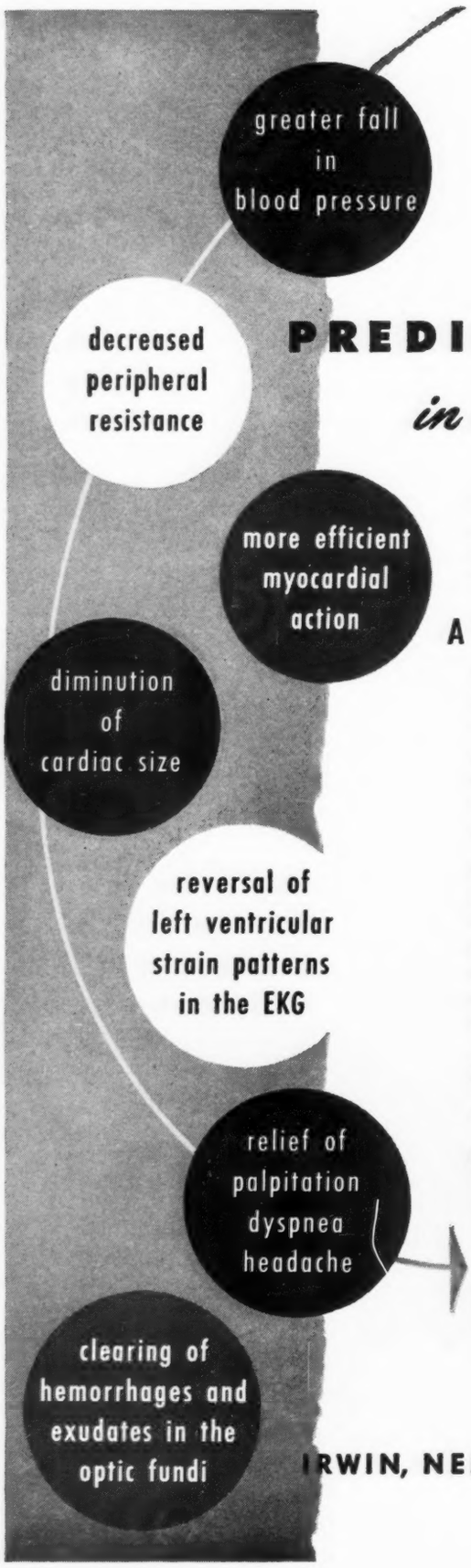

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Perfected after three years of research by Rystan Company, originator of therapeutic water-soluble chlorophyll preparations, this combination product assures prolonged contact of *tissue-stimulating* chlorophyll with the ulcer crater.

Clinical evidence shows that it offers six distinct advantages:

1. Promotes healthy granulation tissue at the ulcer site.

2. Gives prompt symptomatic relief.

3. Provides a prolonged protective coating.

4. Provides prompt antacid action—no alkalosis, no acid rebound, no interference with bowel regularity.

5. Completely safe, absolutely nontoxic.

6. Minimizes—often eliminates—need for special diets and restricted activity.

How it works

A three-way combination product, Chloresium Powder provides the antacid and protective actions of the usual peptic ulcer preparations with aluminum hydroxide and magnesium trisilicate in a specially prepared dehydrated okra base. *The addition of the water-soluble derivatives of chlorophyll "a" gives you a healing therapy that actually promotes healthy granulation tissue at the ulcer site.*

"The high incidence of patients who have gone through one ulcer regimen after another with temporary relief, but with no healing of the ulcer crater, suggests the need of supplying direct assistance to the damaged gastroduodenal[1] tissues in the form of a tissue-stimulant."

Chloresium Powder provides prolonged contact of tissue-stimulating chlorophyll *with the ulcer crater.*

therapy for peptic ulcers!

Dramatic results in long-standing peptic ulcer cases

In a recently reported clinical series[1], complete healing was obtained in 58 out of 79 cases of *long-standing* peptic ulcers within 2 to 7 weeks—with this new chlorophyll powder!

Chloresium Powder, in this clinical trial, demonstrated its effectiveness to the peptic ulcer patient quickly in the form of complete symptomatic relief. It demonstrated its effectiveness to the physician, under roentgenological examination, in prompt healing of the ulcer crater—usually in 2 to 7 weeks—even in cases which had been resistant to other therapy.

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To avoid factors whose beneficial effects might be difficult to disassociate from the effects of the Chloresium Powder, no special diets were prescribed. There were no restrictions on smoking, alcoholic beverages or daily activity. Nevertheless, 3 out of 4 cases not only got lasting symptomatic relief in 1 to 3 days, but also obtained *complete healing of the ulcers* in 2 to 7 weeks.

These remarkable results—obtained with complete freedom from dietary and other restrictions—indicate that here at last is a therapy which can be administered without upsetting the patient's normal habits and can thus greatly simplify the task of insuring patient co-operation. Moreover, Chloresium Powder is palatable and easily taken by the patient.

1. Offenkrantz, W. F., *Rev. Gastroenterol*, 17:359-367 (May), 1950.

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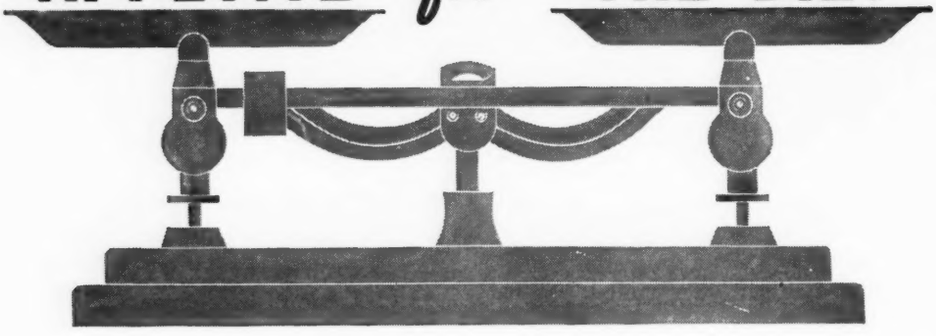

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REFERENCES: Ray, H. M.: Am. J. Digest. Dis., *14*:153, 1947.
Shapiro, S.: ibid, *14*:261, 1947.

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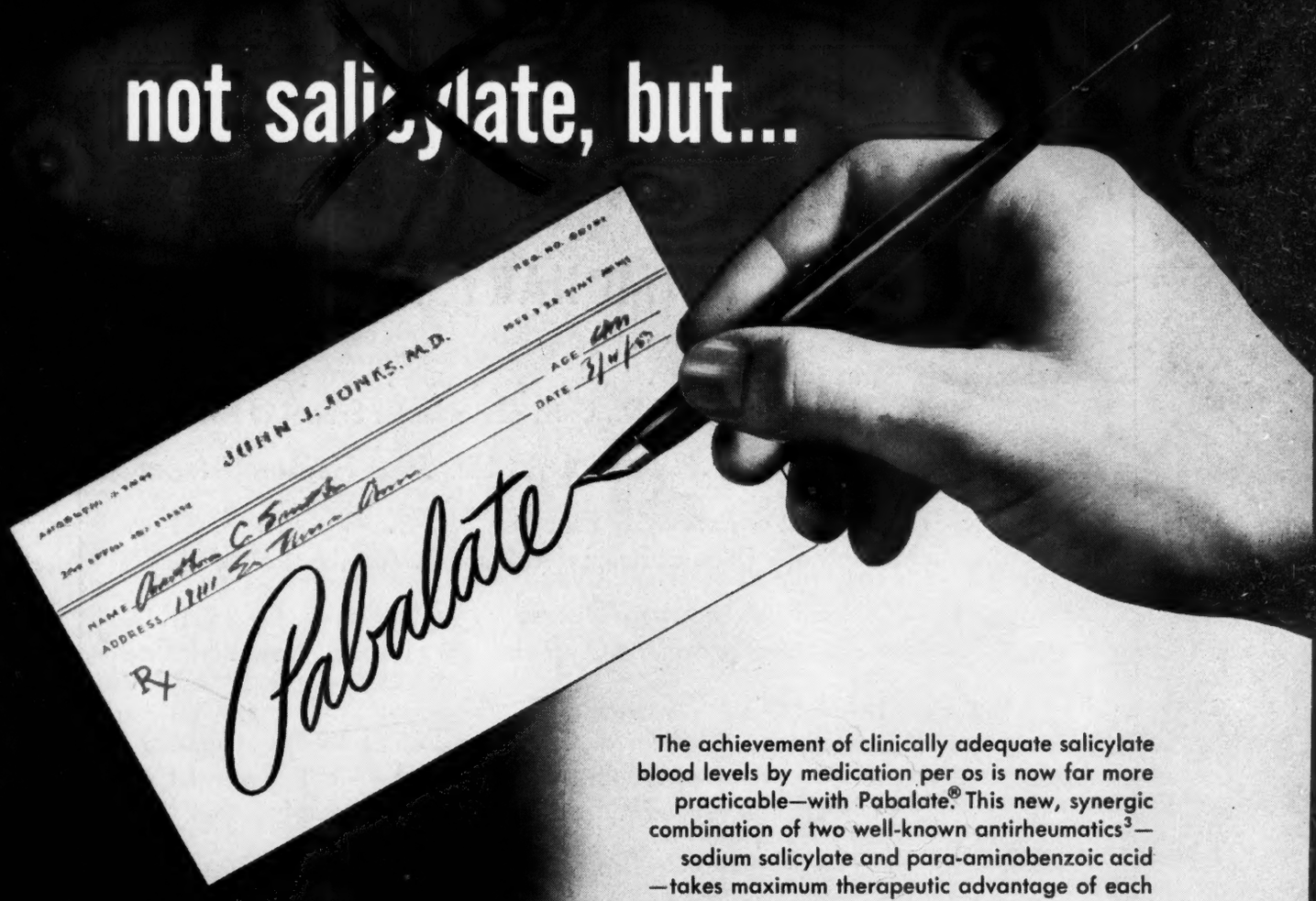

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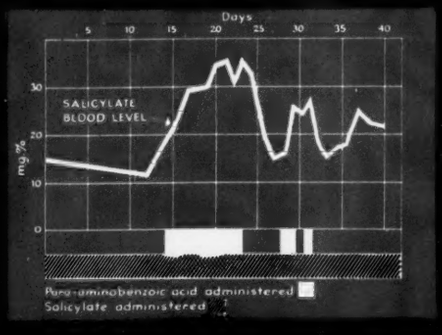

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SUPPLIED: Pabalate Tablets in bottles of 100 and 500. Pabalate Liquid in pints and gallons.

REFERENCES: 1. Belisle, M.: Union Med. Can., 77:392, 1948. **2.** Dry, I. J. et al.: Proc. Staff Meetings Mayo Clin., 21:497, 1946. **3.** Rosenblum, H. and Fraser, L. E.: Proc. Soc. Exper. Biol. and Med., 65:178, 1947. **4.** Salassa, Bollman and Dry: J. Lab. Clin. Med., 33:1393, 1948.

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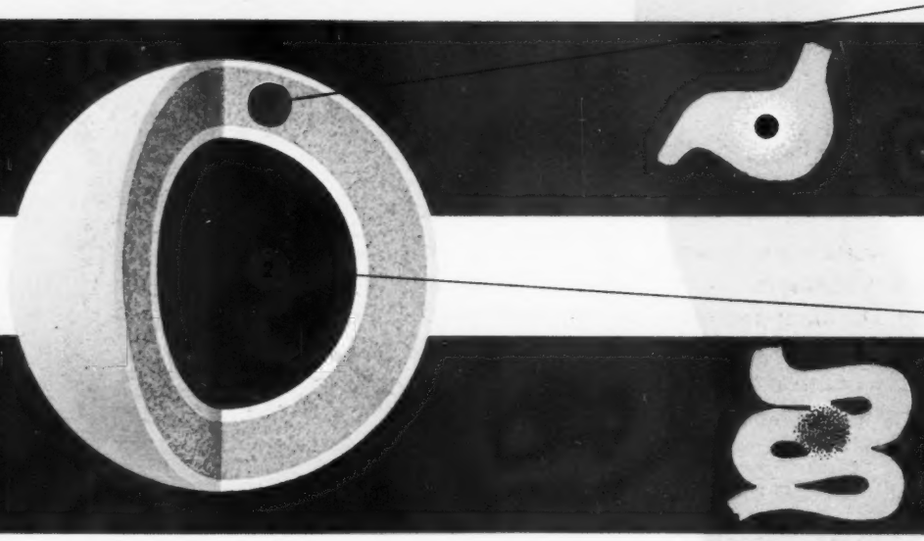

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references

1. McGavack, T. H., and Klotz, S. D.: Bull. Flower Fifth Ave. Hosp., 9:61, 1946. 2. Weissberg, J., et al.: Am. J. Digest Dis., 15:332, 1948.

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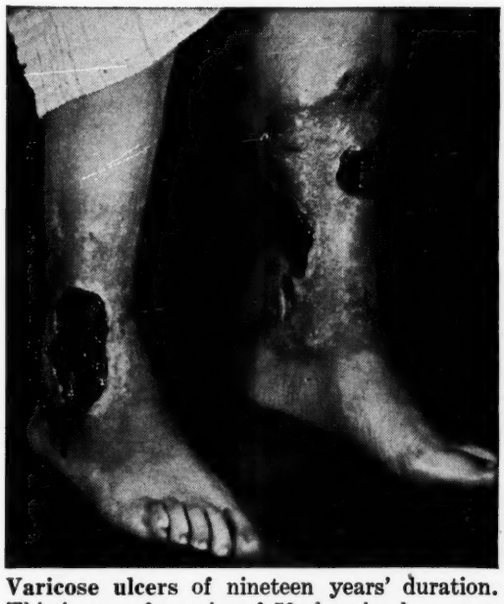
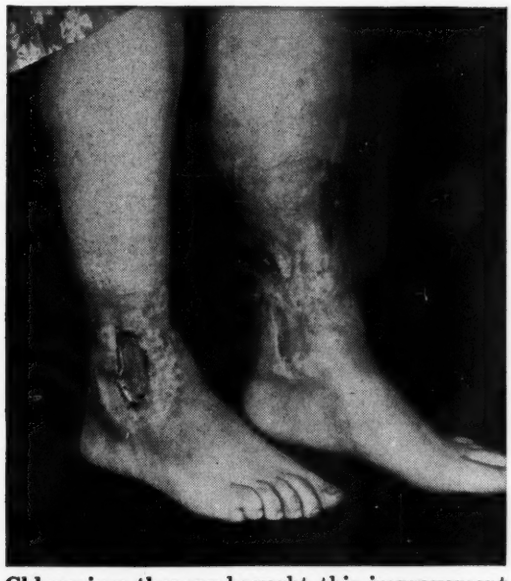


Varicose ulcers of nineteen years' duration. This is one of a series of 50 chronic ulcer cases in which the results of Chloresium Therapy were observed by a leading clinic.



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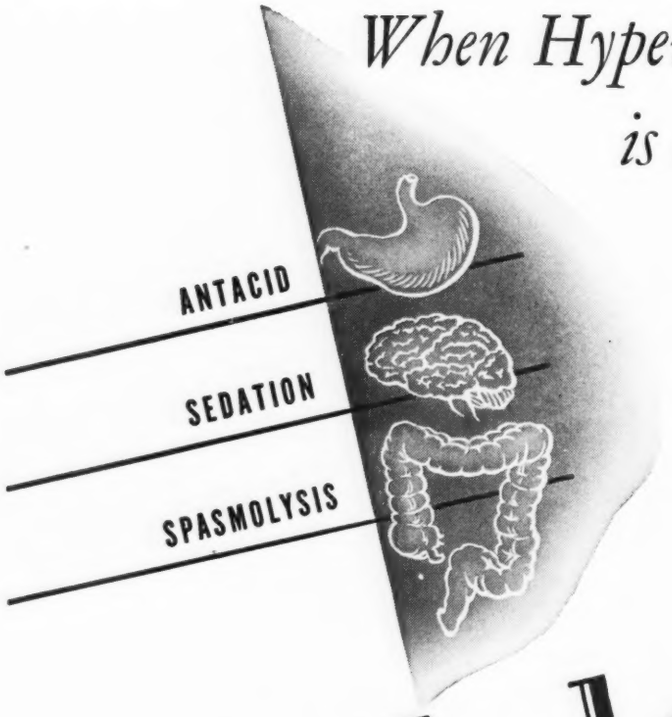

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While individualization of dosage is essential for maximum therapeutic benefit, in the majority of patients a response to Veriloid is usually obtained from the average dose of 2.0 mg. to 5.0 mg. three or four times daily after meals and at bedtime. Dosage adjustment to suit the responsiveness of the individual patient can be accomplished in a week or two.

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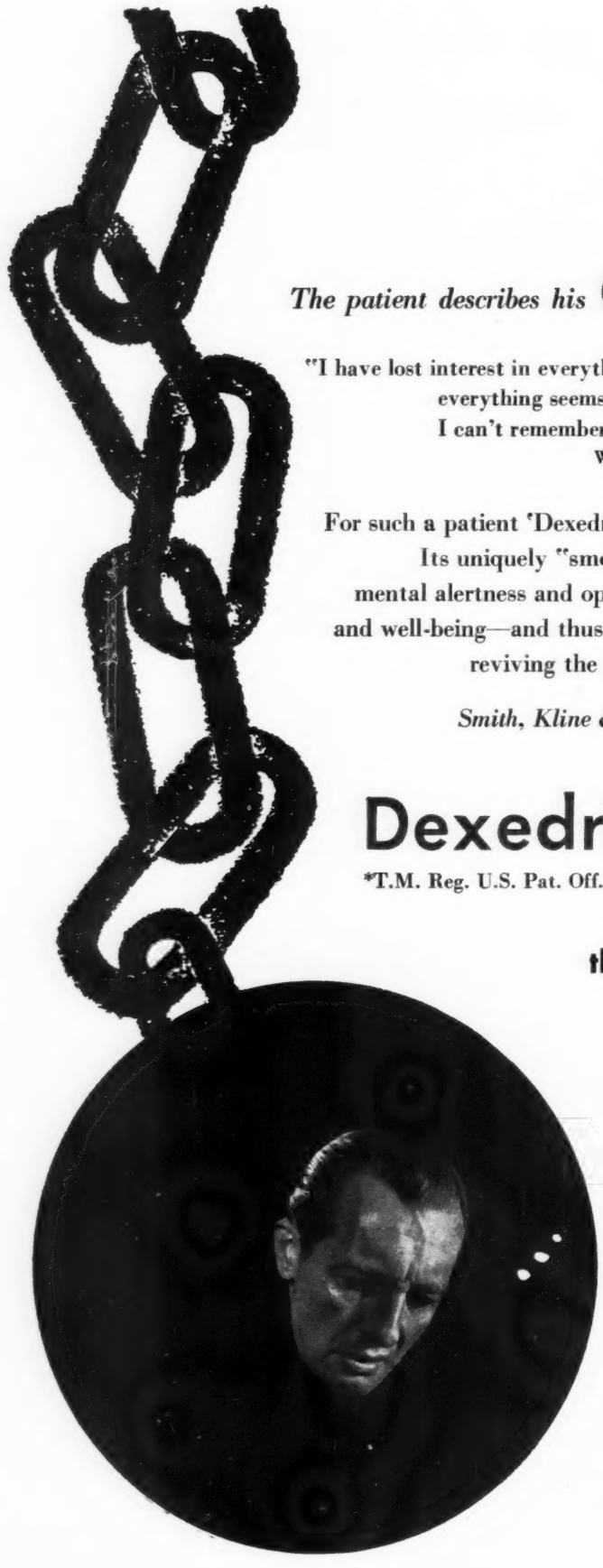

The patient describes his **depression:**

"I have lost interest in everything—I have no ambition any more—
everything seems futile—I feel frustrated and lonely—
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Washburne, A.C.: Ann. Int. Med. *32*:265, 1950.

For such a patient 'Dexedrine' Sulfate is of unequalled value. Its uniquely "smooth" antidepressant effect restores mental alertness and optimism, induces a feeling of energy and well-being—and thus has the happy effect of once again reviving the patient's interest in life and living.

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The American Journal of Medicine

VOL. IX OCTOBER, 1950 No. 4

Editorial

Cerebral Blood Flow and Metabolism*

KETY and Schmidt[1] opened a new field of clinical investigation when they demonstrated that the blood flow per 100 gm. of brain could be measured in normal man by an application of the Fick principle. The subject breathes for ten minutes a non-anesthetic gas mixture composed of 15 per cent N_2O, 21 per cent O_2 and 64 per cent N_2. The mean N_2O difference between arterial and internal jugular bloods is calculated from samples drawn simultaneously from the two vessels over the ten-minute period of time. At the end of ten minutes the brain has come into equilibrium with the internal jugular blood, and the concentrations of N_2O in the arterial blood, internal jugular blood and brain are approximately equal. N_2O has the same solubility in blood and brain in normal subjects. Therefore, the amount of N_2O deposited per 100 gm. of brain during the ten-minute period of time is equal to the concentrations of N_2O per 100 cc. of internal jugular blood. The cerebral blood flow per 100 gm. of brain is then calculated by the Fick formula:

$$\text{CBF} = \frac{\text{N}_2\text{O deposited}}{\text{A-V N}_2\text{O difference}}.$$

The A-V N_2O difference is not constant during the ten minutes of breathing N_2O. At the start it is zero; then it becomes large for a variable period of time, and before the end of ten minutes has approached zero. Different technics have been used to obtain the mean A-V N_2O difference over the entire ten-minute period of breathing N_2O. Kety and Schmidt have taken multiple simultaneous samples and constructed curves for the arterial and venous concentrations of N_2O. The A-V difference is calculated from the area between the curves. Scheinberg and Stead[2] have drawn, at a constant rate, continuous samples of arterial and venous bloods over the ten-minute period of breathing. The mean A-V N_2O difference per minute is obtained by subtracting the N_2O concentration of the venous sample from that of the arterial sample and dividing by 10. Although the absolute values for cerebral blood flow obtained by the continuous sampling technic have been higher than those reported by Kety and Schmidt, consistent results are obtained by either method. It should be emphasized that the blood flow is measured per 100 gm. of brain and that the method gives no information as to the total blood flow through the brain. If one-half the brain were removed and the function of the remainder unaltered, the value for cerebral blood flow as determined above should be unchanged.

[1] KETY, S. S. and SCHMIDT, C. F. Determination of cerebral blood flow in man by use of nitrous oxide in low concentrations. *Am. J. Physiol.*, 143: 53, 1945.

[2] SCHEINBERG, P. and STEAD, E. A., JR. The cerebral blood flow in male subjects as measured by the nitrous oxide technique. Normal values for blood flow, oxygen utilization, glucose utilization, and peripheral resistance, with observations on the effect of tilting and anxiety. *J. Clin. Investigation*, 28: 1163, 1949.

* From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

The oxygen consumption and the glucose consumption per 100 gm. of brain are calculated by measuring the respective arterial-internal jugular differences and multiplying them by the cerebral blood flow. The respirator quotient is calculated from oxygen and carbon dioxide analyses on samples of arterial and internal jugular blood.

The brain in the resting, fasting state receives about 14 per cent of the cardiac output. The cerebral blood flow is relatively constant in normal subjects and is not increased by apprehension,[2] by stellate ganglion block[3,4] or by flushing doses of nicotinic acid.[5] It is decreased in normal subjects by motionless standing[2] and during hyperventilation,[6] and in patients with myxedema,[7] pernicious anemia,[8] cerebral arteriosclerosis[4] and heart failure.[9] In cerebral arteriosclerosis the reduction of blood flow occurs before there is any change in cerebral metabolic rate. As the process advances, cerebral metabolic rate is reduced. In heart failure the usual reduction in cardiac output is accompanied by a proportionate reduction in cerebral blood flow. The increase in peripheral resistance seen in heart failure does not spare the cerebral circulation. The cerebral blood flow is increased by uncomplicated anemia and by breathing CO_2.

The arterial-internal jugular oxygen difference is approximately 6 vols. per cent. As the arterial-mixed venous oxygen difference of the body is about 4 vols. per cent, the brain extracts more oxygen per unit of blood than does the body as a whole. It uses approximately 20 per cent of the oxygen taken in by the lungs.

As yet no data are available on means of increasing the cerebral metabolism above the level found in the normally alert subject. Fever[10] and thyrotoxicosis[11] do not increase cerebral metabolism. In patients with myxedema, advanced pernicious anemia, severe heart failure and advanced arteriosclerotic disease of the brain the cerebral oxygen consumption is quantitatively reduced. Qualitatively, the brain continues to utilize glucose as its source of energy and the glucose:oxygen ratio remains at the same value.

The respiratory quotient of the brain is very close to unity. The brain normally obtains its energy from the breakdown of glucose. Because of the direct utilization of glucose from the blood stream there is a constant ratio between the cerebral arteriovenous oxygen and glucose differences. The ratio is not equal to the theoretic ratio, which would be present if glucose were completely oxidized to CO_2 and water, because a small amount of glucose appears in the cerebral venous blood as lactic and pyruvic acids. In the resting, fasting state the average person delivers into the hepatic vein about 112 mg. of glucose per minute.[12] Of this the brain uses 78 mg., or 70 per cent, leaving only 34 mg. per minute for the rest of the non-splanchnic tissues.

Patients with pernicious anemia and the familiar neurologic picture of combined system disease are of particular interest be-

[2] For footnote see page 425.

[3] HARMEL, M. H., HAFKENSCHIEL, J. H., AUSTIN, G. M., CRUMPTON, C. W. and KETY, S. S. The effect of bilateral stellate ganglion block on the cerebral circulation in normotensive and hypertensive patients. *J. Clin. Investigation*, 28: 415, 1949.

[4] SCHEINBERG, P. Cerebral blood flow in vascular disease of the brain, with observations on the effect of stellate ganglion block. *Am. J. Med.*, 8: 139, 1950.

[5] SCHEINBERG, P. The effects of nicotinic acid on the cerebral circulation with observations of extra-cerebral contamination of internal jugular blood in the nitrous oxide procedure of cerebral blood flow. *Circulation*, 1: 1148, 1950.

[6] KETY, S. S. and SCHMIDT, C. F. The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output and blood pressure of normal young men. *J. Clin. Investigation*, 27: 476, 1948.

[7] SCHEINBERG, P. Cerebral metabolism in hyperthyroidism and myxedema. *Federation Proc.*, 9: 113, 1950.

[8] SCHEINBERG, P. Cerebral metabolism in pernicious anemia. *J. Clin. Investigation*, 29: 843, 1950.

[9] SCHEINBERG, P. The cerebral circulation in congestive heart failure. *Am. J. Med.*, 8: 148, 1950.

[10] PATTERSON, J. Personal communications.

[11] SCHEINBERG, P. Cerebral circulation and metabolism in hyperthyroidism. (To be published in *J. Clin. Investigation.*)

[12] MYERS, J. D. Net splanchnic glucose production in normal man and in various disease states. (To be published in *J. Clin. Investigation.*)

cause they show, on the one hand, the effects of anemia on the cerebral circulation, and on the other, the effects of the deficiency state on cerebral metabolism. When the hemoglobin level falls below 7 gm., the circulation to the brain is usually increased. That this is the effect of the anemia itself is shown by the slowing of the circulation as the anemia is corrected. Irrespective of whether severe anemia develops, the deficiency state present in untreated pernicious anemia will eventually cause a decrease in cerebral metabolism because of injury to the cells of the central nervous system. This injury is not reversible in many instances by treatment with liver extracts or vitamin B_{12}. In such patients the level of the cerebral blood flow is moderately increased when the hemoglobin level falls below 7 gm. but becomes abnormally slow when the anemia is corrected. The cerebral metabolism remains depressed in both the anemic and non-anemic states.

There is no simple correlation between the degree of depression of cerebral metabolic rate and the mental status. Ambulatory patients with pernicious anemia may have their cerebral metabolism depressed below the level of patients with diabetic coma. It is interesting to speculate on the causes for this difference in mental status. In diabetic acidosis the metabolism of all the brain cells is probably depressed. In chronic pernicious anemia a part of the neurons may be damaged or have died, and the metabolism of the remainder may be more nearly normal than that of any cells in the presence of diabetic coma. It is possible that an overall depression of metabolism caused by the loss of certain nerve cells but with a normal function of the remaining cells is better tolerated than a slowing of metabolism of a similar degree when no nerve cells have died but all are functioning abnormally.

EUGENE A. STEAD, JR., M.D.

Clinical Studies

Effects of Diet in Essential Hypertension*

I. Baseline Study: Effects in Eighty-six Cases of Prolonged Hospitalization on Regular Hospital Diet

DONALD M. WATKIN, M.D., HERMAN F. FROEB, M.D., FREDERICK T. HATCH, M.D. *and* ALEXANDER B. GUTMAN, M.D.

New York, New York

A PREREQUISITE to evaluation of any form of management of essential hypertension is an appreciation of the vagaries of the natural history of the disease. Obviously, the fluctuations in blood pressure and other manifestations which may occur spontaneously during the period of treatment or as the result of hospitalization *per se* should not be attributed to the specific effects of therapy. Surprisingly little precise data on this aspect of essential hypertension are available however.

In the course of observations during the control period preceding trial of the rice diet and related forms of dietary management of hypertension we have accumulated a considerable body of data concerning the effects of hospitalization on a standardized regular hospital diet. Recorded here are observations on symptomatology, blood pressure, heart size, electrocardiographic findings and retinopathy; other relevant control data will be included in our report on the effects of the rice diet[1] or in separate communications. The data presented provide baseline points of reference for general evaluation of the effects of any allegedly specific form of therapy in hypertension.

MATERIAL AND METHODS

Selection of Patients. Between July, 1948, and March, 1950, 105 patients with marked hypertension were admitted to this Service for study. They were selected from a total of approximately 900 patients interviewed and examined at various New York City hospitals and clinics. Patients were chosen with the view of instituting the rice diet after a suitable control period; and since it was our intention to give the rice diet a rigorous trial, only the most severe cases of essential hypertension available to us were admitted. Preference was therefore given to patients with very marked hypertension, rapidly progressive manifestations of malignant hypertension and objective evidences of advanced hypertensive cardiovascular disease. The minimal acceptable blood pressure was 220/120 mm. Hg, except in a few instances presenting other features of interest. All patients agreed to remain in the hospital under observation for four to six months.

Of the 105 patients admitted, 19 were excluded from this study. Of these, seven died within two weeks of admission. Six were found to have chronic glomerulonephritis as the cause of their hypertension. Five, although exhibiting marked hypertension on acceptance in other hospitals or clinics, showed normal blood pressures after one or two days on this Service. One patient's course was disrupted by so many episodes of cardiac arrhythmia that interpretation of blood pressure changes was impossible.

The remaining eighty-six patients with essential hypertension constitute the subject of this report. Their medical background is indicated by the following tabulation of major complications recorded in various hospitals and clinics prior to admission to this Service:

* From the Columbia Research Service, Goldwater Memorial Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York City. This investigation was supported (in part) by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, U. S. Public Health Service, and by a grant from the Lasker Foundation.

	No. of Patients
Abnormal electrocardiogram*	59
Myocardial infarction	7
Advanced retinopathy	33
Keith-Wagener-Barker grade III	23
Keith-Wagener-Barker grade IV	10
Congestive failure	31
Cerebrovascular accidents	16
Hemiplegia	13
Diffuse lesions	2
Athetosis	1
Marked renal insufficiency (BUN > 50 mg. %)	4
Hypertensive encephalopathy	2

* Exclusive of electrocardiograms showing digitalis effects.

Standardization of Activity, Medication and Diet. Upon admission the patients were confined to bed with lavatory privileges for the first three weeks; then, if their condition permitted ambulation, they were allowed up for participation in regular ward activities. Medications such as digitalis, mercurial diuretics and sedatives were discontinued whenever possible. All patients were placed on a standard control diet of the following daily composition:

	Calculated (gm.)	Analysis (gm.)*
Protein	80	85.6 (13.7 N × 6.25)
Fat	85	.....
Carbohydrate	275	.....
Sodium	2.2	3.98 (173 mEq.)
Potassium	3.5	3.60 (92 mEq.)
Calcium	1.0	.....
Phosphorus	1.2	.....
Iron	0.02	.....
Chloride	1.9	.....
Fluid	2500 ml.	.....
Calories	2185	.....

* N determined by macro-Kjeldahl technic. Na and K were determined by internal standard flame photometer after dry ashing. The figures cited are the means of several analyses.

Weights were recorded daily. The mean change in weight over the period of this study was +0.3 kg., varying from +5.7 to −4.9.

Hospital Work-up. Routine work-up of each patient included detailed history and physical examination, basal blood pressures, funduscopy, heart size in 2-meter films, electrocardiogram, gastrointestinal x-ray series, basal metabolism, venous pressure, circulation time, amytal and cold pressor tests, erythrocyte sedimentation rate, hematologic examination, urinalyses, PSP excretion, urea clearance, serum urea N or NPN, fasting blood sugar, glucose tolerance, serum cholesterol and cholesterol esters (Schoenheimer-Sperry method), phospholipids and neutral fat (Kendall-Davidson), total proteins, albumin and globulins (Howe method), sodium and potassium (by internal standard flame photometer), carbon dioxide content, calcium and phosphorus. When indicated, such additional examinations as benzodioxane test, eyeground photography, estimation of plasma volume, glomerular filtration rate (inulin), renal blood flow (PAH), Tm_{PAH} were made. In addition, a number of special studies were carried out for comparison with the rice diet period, as will be noted in our report on the effects of the rice diet.[1]

Method of Taking and Recording Blood Pressure. Blood pressure measurements were made by assigned physicians and nurses with a mercury sphygmomanometer three times weekly in each patient before rising in the morning. Six successive readings at approximately thirty-second intervals were made. The lowest systolic and the lowest diastolic pressure reading of the six obtained was recorded as the basal pressure for that day. The three basal systolic and diastolic pressures for each week were averaged, recorded as the mean basal pressures for that week and used for further analysis.

Basal blood pressure levels are not, of course, representative of the patients' blood pressure levels throughout the day. However, they minimally reflect pressor responses associated with the act of recording the blood pressure and with other extraneous environmental factors. The blood pressure changes observed would therefore seem to have most significance in interpreting the objective effects of hospitalization, diet and other factors which were our principal interest. Actually, as the table on page 430 indicates, we found that the mean basal blood pressure for a given week often was not appreciably lower than the mean of all the blood pressure readings recorded the same week.

Heart Size Measurements. Changes in heart size were calculated from measurements of the maximal transverse projection of the cardiac silhouette (in maximal inspiration) in 2-meter films obtained at the beginning and end of the period of hospitalization on a regular hospital diet. For the sake of uniformity, all measurements were made by the same physician. The predicted transverse diameter of the heart was calculated from tables of height and weight.[2]

Electrocardiograms. Electrocardiograms were made with a standard Cambridge string-gauge galvanometer repeatedly at intervals of four to six weeks. The three standard limb leads and V5 were recorded. Standardization of all tracings was checked. Patients recently receiving digitalis or still on digitalis therapy were not included in the analysis of electrocardiograms.

Patient	Age and Sex	Basal B.P.	Mean B.P.
A. A.	65 M	197/107	201/110
H. Col.	47 M	202/109	204/112
R. C.	48 M	180/115	185/118
H. F.	53 M	183/93	204/95
C. H.	40 M	164/116	167/122
S. La.	60 M	172/104	179/113
B. P.	41 M	175/109	186/120
G. R.	54 M	208/122	211/125
F. Ru.	40 M	172/123	178/126
M. Ba.	40 F	224/158	236/160
M. Be.	57 F	152/100	155/105
Ma. C.	61 F	192/85	204/93
J. Co.	32 F	202/104	211/108
D. K.	48 F	161/111	163/111
M. Kn.	57 F	190/91	201/96
S. Lau.	26 F	225/129	232/136
I. Mu.	48 F	214/120	220/123
H. O.	45 F	240/135	248/137
H. S.	51 F	214/105	216/109
	Mean:	193/112	200/117

Retinopathy. Examination of eyegrounds was made by consultant ophthalmologists at repeated intervals during the period of hospitalization, for the sake of uniformity usually by the same consultant in individual patients. The Keith-Wagener-Barker classification of retinopathy was employed.[3]

RESULTS

Symptomatology. Table I summarizes the presenting complaints of the patients on admission to this Service and again at the end of the period of hospitalization on a standardized regular diet (mean period of observation: 9.3 weeks). The number and percentage of patients showing improvement in each category is indicated. Obviously, evaluation of largely subjective manifestations is difficult and any estimate of improvement is open to large error. Nevertheless a significant proportion of patients, varying from approximately 25 to 50 per cent in different categories, clearly derived substantial symptomatic benefit from the general measures employed. As might be anticipated, this improvement was most frequent in respect to manifestations of cardiac decompensation. On the other hand, severe and often incapacitating headaches associated with hypertension were apt to persist in spite of improvement in other respects. It will be noted that six of our patients became completely asymptomatic in addition to those without subjective complaints referable to hypertensive cardiovascular disease at the time of admission.

Of the patients who showed no symptomatic improvement during the period of hospitalization, three showed rapid progression of the disease under observation. These three (all in the malignant phase of essential hypertension) died—two in uremia and the third of subarachnoid hemorrhage. These deaths are in addition to the seven occurring within two weeks of admission and excluded from our series.

Blood Pressure. Table II summarizes the data on basal blood pressure levels in eighty-six patients with essential hypertension. A comparison is made of four periods of observation. The *mean basal acceptance blood pressure* is that recorded in various clinics or hospitals by one of us when examining the patient for acceptance to this hospital, and represents the lowest systolic and the lowest diastolic reading of four to six readings with the patient at rest in the recumbent position. The *basal blood pressure on admission* is the lowest systolic and diastolic pressure recorded on the first or second day of admission. The mean basal blood pressures for the *first week of hospitalization* and the mean of the lowest systolic and diastolic pressures recorded during the *final three weeks of hospitalization* on a standardized regular hospital diet are also recorded for each patient. The duration of hospitalization (mean: 9.3 weeks) is indicated in the last column.

Analysis of the differences in basal blood pressure at these four periods of observation

in the same patient is of considerable interest in pointing up fallacies in interpretation of the effects of various therapeutic regimens. Often a comparison is made with blood pressure readings in other hospitals or clinics, here represented by our acceptance levels recorded (−83/−58, −88/−66, −52/−33 mm. Hg in cases E. R., An. Wa., L. Smk., respectively). In some such instances the drop in diastolic pressure was as striking as that in systolic, occasionally more so.

TABLE I

PRESENTING SYMPTOMS IN EIGHTY-SIX PATIENTS WITH ESSENTIAL HYPERTENSION AND INCIDENCE OF SYMPTOMATIC IMPROVEMENT AFTER PROLONGED HOSPITALIZATION

Symptom	On Admission				At End of Observation				Improved	
	Males	Females	Total	Per cent of 86 Cases	Males	Females	Total	Per cent of 86 Cases	No. of Patients	Per cent
Severe headaches	17	22	39	45	13	16	29	34	10	26
Dyspnea	16	18	34	40	10	9	19	22	15	44
Orthopnea	8	9	17	20	8	4	12	14	5	29
Dizziness	6	10	16	19	5	6	11	13	5	31
Edema	6	7	13	15	1	5	6	7	7	54
Heart consciousness	3	7	10	12	3	5	8	9	2	20
Paralysis from cerebral vascular accident	6	6	12	14	6	6	12	14	0	0
Nausea and vomiting	1	5	6	7	1	3	4	5	2	33
Angina pectoris	1	4	5	6	1	2	3	3	2	40
Failing vision	1	4	5	6	1	4	5	6	0	0
Disorientation	2	2	4	5	2	1	3	3	1	25
Asymptomatic	6	3	9	10	9	6	15	17	..	..

blood pressures. Frequently the blood pressures obtained on the first day or two of admission are employed as a baseline for evaluation of therapy. Inspection of the data in Table II reveals that both practices may lead to large error.

Striking differences were found to occur between the *acceptance blood pressures* (mean: 227/129 mm. Hg) and the basal blood pressures obtained both on the *first* or *second day of admission* to this Service and during the *first week of hospitalization* (means: 202/114 and 200/112, respectively). The differences between these means (−25/−15 and −27/−17 mm. Hg, respectively) are large but nevertheless do not adequately reflect the extraordinary and unpredictable variations encountered in individual cases. Comparing acceptance blood pressures with the mean of readings in the first week of hospitalization, for example, many patients showed a remarkable fall in both systolic and diastolic basal blood pressure

Falls in basal blood pressure of this magnitude were encountered even in patients well known to us in our outpatient clinic. Case M. T. was a woman fifty-five years of age whose basal blood pressure was recorded by one of us on seven different occasions over a period of three months as follows: 228/108, 190/100, 210/100, 240/105, 230/110, 230/110 and 220/108 mm. Hg. The first basal blood pressure reading obtained after admission to the hospital was 153/88 and the mean of the basal blood pressures recorded during the first week was 170/93 mm. Hg.

By way of contrast, examination of Table II will reveal many instances in which the differences between systolic and/or diastolic blood pressures on acceptance and in the first week of hospitalization were insignificant and a few in which there were significantly increased levels.

Comparison of basal blood pressure readings recorded on the *first day* or two of admission to this Service with the mean basal levels for the *first week* in the hospital discloses large and unpredictable differences

TABLE II

EFFECTS OF PROLONGED HOSPITALIZATION (STANDARDIZED REGULAR HOSPITAL DIET) ON BASAL BLOOD PRESSURE OF EIGHTY-SIX PATIENTS WITH ESSENTIAL HYPERTENSION

Patient	Age and Sex	Known Duration of Hypertension (yr.)	Mean Basal Blood Pressure Levels						Duration of Hospitalization (wk.)
			On Acceptance (*a*) (mm. Hg)	On Admission (*b*) (mm. Hg)	First Week (*c*) (mm. Hg)	Δ *a* − *c* (mm. Hg)	Final Three Weeks (*d*) (mm. Hg)	Δ *c* − *d* (mm. Hg)	
A. A.	65 M	2	210/115	200/118	196/113	− 14/− 2	196/109	± 0/− 4	15
C. A.	58 M	10	220/120	186/100	197/107	− 23/−13	191/105	− 6/− 2	11
Mu. C.	57 M	3	204/100	220/105	199/ 99	− 5/− 1	188/ 96	−11/− 3	12
H. Col.	47 M	5	214/114	228/124	222/111	+ 8/− 3	214/111	− 8/± 0	8
R. C.	48 M	11	204/148	212/126	203/119	− 1/−29	181/113	−22/− 6	7
A. Co.	46 M	0.5	230/160	190/130	190/130	− 40/−30	218/142	+28/+12	10
S. D.	52 M	13	254/148	202/116	209/118	− 45/−30	215/133	+ 6/+15	9
D. D.	38 M	8	220/160	182/130	191/133	− 29/−27	197/141	+ 6/+ 8	7
A. D.	44 M	2	190/125	208/124	191/116	+ 1/− 9	170/107	−21/− 9	9
H. F.	53 M	4	240/120	202/ 92	196/ 93	− 44/−27	191/ 90	− 5/− 3	13
R. G.	53 M	4	240/130	223/120	220/113	− 20/−17	207/117	−13/+ 4	8
F. H.	49 M	5	230/110	198/104	209/112	− 21/+ 2	208/107	− 1/− 5	6
C. H.	40 M	7	180/120	160/110	175/121	− 5/− 1	163/113	−12/− 8	16
W. H.	59 M	20	185/105	196/ 98	215/107	+ 30/+ 2	203/104	−12/− 3	11
H. H.	67 M	10	220/ 98	198/ 88	199/ 88	− 21/−10	177/ 79	−22/− 9	6
P. K.	59 M	1	175/111	163/115	171/117	− 4/+ 6	150/ 97	−21/−20	20
G. K.	48 M	?	220/120	244/118	244/118	+ 24/− 2	226/128	−18/+10	7
C. La.	54 M	1.5	230/120	228/106	201/ 97	− 29/−23	205/ 93	+ 4/− 4	8
S. La.	60 M	2	180/130	167/109	182/117	+ 2/−13	176/105	− 6/−12	6
B. L.	60 M	2	320/150	222/116	218/113	−102/−37	215/ 84	− 3/−29	12
T. Mc.	46 M	3	230/140	220/126	221/120	− 9/−20	200/140	−21/+20	6
J. Mc.	42 M	10	218/136	218/136	162/103	− 56/−33	180/119	+18/+16	6
D. Mc.	56 M	12	220/140	186/132	179/117	− 41/−23	195/131	+16/+14	7
Al. Ma.	59 M	5	208/130	188/125	188/121	− 20/− 9	167/110	−21/−11	6
F. M.	40 M	0.3	250/150	219/140	214/148	− 36/− 2	214/150	± 0/+ 2	3
S. N.	52 M	10	225/145	218/120	210/126	− 15/−19	191/113	−19/−13	6
B. P.	41 M	19	240/130	220/130	210/129	− 30/− 1	174/112	−36/−17	13
E. R.	61 M	15	255/160	224/144	172/102	− 83/−58	170/ 96	− 2/− 6	10
G. R.	54 M	5	210/140	210/124	205/130	− 5/−10	205/121	± 0/− 9	10
C. Ro.	49 M	7	225/122	180/100	183/100	− 42/−22	201/109	+18/+ 9	11
F. Ru.	40 M	1	220/120	180/126	181/124	− 39/+ 4	172/121	− 9/− 3	14
M. Sl.	50 M	5	265/120	205/ 74	208/ 83	− 57/−37	215/ 93	+ 7/+10	4
F. Sm.	64 M	7	240/110	176/ 90	204/ 97	− 36/−13	200/101	− 4/+ 4	15
S. S.	45 M	8	206/126	215/132	208/128	+ 2/+ 2	207/131	− 1/+ 3	7
W. Su.	29 M	10	220/100	166/112	172/115	− 48/+15	196/130	+14/+15	6
L. T.	49 M	4	180/130	178/120	178/120	− 2/−10	187/128	+ 9/+ 8	7
G. W.	48 M	1.5	210/110	164/ 88	172/ 93	− 38/−17	159/ 89	−13/− 4	14
Ab. Wa.	53 M	12	230/120	198/104	198/104	− 32/−16	186/114	−12/+10	6
M. Ba.	40 F	4	240/160	236/149	227/147	− 23/−13	224/152	− 3/+ 5	9
F. B.	55 F	2.5	210/104	187/104	191/104	− 19/± 0	197/105	+ 6/+ 1	7
M. Be.	57 F	14	222/130	166/122	171/122	− 51/− 8	153/ 99	−18/−23	9
D. B.	38 F	2	190/120	164/103	154/ 94	− 36/−26	148/ 95	− 6/+ 1	7
C. B.	63 F	1	260/130	248/124	248/124	− 12/− 6	171/ 84	−77/−40	11
S. C.	37 F	7	200/125	158/108	166/108	− 34/−17	173/108	+ 7/± 0	3
J. Cl.	50 F	10	220/110	204/110	202/103	− 18/− 7	200/ 98	− 2/− 5	12
Ma. C.	61 F	9	230/130	254/114	223/ 99	− 7/−31	224/ 96	+ 1/− 3	13
J. Co.	32 F	1.5	228/150	212/130	184/115	− 44/−35	162/111	−22/− 4	8
O. C.	67 F	4	220/140	196/ 95	192/100	− 28/−40	142/ 87	−50/−13	7
C. D.	42 F	17	230/150	221/104	228/116	− 2/−34	243/129	+15/+13	8
A. Fa.	42 F	15	290/160	214/134	226/135	− 64/−25	244/141	+18/+ 6	5

TABLE II.—(*Continued*)

Patient	Age and Sex	Known Duration of Hypertension (yr.)	Mean Basal Blood Pressure Levels						Duration of Hospitalization (wk.)
			On Acceptance (*a*) (mm. Hg)	On Admission (*b*) (mm. Hg)	First Week (*c*) (mm. Hg)	Δ *a* − *c* (mm. Hg)	Final Three Weeks (*d*) (mm. Hg)	Δ *c* − *d* (mm. Hg)	
A. Fe.	54 F	15	230/135	240/112	242/103	+ 12/−32	228/ 84	−14/−19	9
T. F.	51 F	6	230/150	194/120	191/119	− 39/−31	174/ 5	−17/−24	21
E. G.	53 F	1	210/114	248/128	221/125	+ 11/+11	202/122	−19/− 3	7
S. G.	40 F	2	220/110	200/128	182/ 87	− 38/−23	173/ 88	− 9/+ 1	7
S. Ka.	55 F	6	220/120	160/100	156/ 99	− 64/−21	162/ 92	+ 6/− 7	13
D. K.	48 F	7	220/130	160/120	159/100	− 61/−30	165/109	+ 6/+ 9	7
M. Ki.	54 F	16	290/150	230/138	239/133	− 51/−17	237/125	− 2/− 8	8
A. K.	34 F	4	250/130	139/ 90	150/ 93	−100/−37	156/ 88	+ 6/− 5	17
M. Kn.	57 F	30	220/130	220/ 96	215/ 93	− 5/−37	187/ 92	−28/− 1	12
S. Kr.	54 F	5	290/130	256/110	245/105	− 45/−25	245/106	+ 9/+ 1	5
A. L.	51 F	23	237/121	206/120	206/120	− 31/− 1	204/116	− 2/− 4	8
S. Lau.	26 F	5	250/140	240/135	230/124	− 20/−16	239/137	+ 9/+13	15
C. Lo.	33 F	13	220/130	190/ 98	192/106	− 28/−24	190/109	− 2/+ 3	8
An. Ma.	49 F	20	260/145	236/136	235/137	− 25/− 8	208/122	−27/−15	8
A. Man.	44 F	11	185/100	213/116	208/109	+ 23/+ 9	203/115	− 5/+ 6	3
E. M.	70 F	4	240/120	212/ 98	203/ 94	− 37/−26	191/ 89	−12/− 5	13
A. Mo.	40 F	4	210/140	198/126	219/130	+ 9/−10	206/122	−13/− 8	8
I. Mu.	48 F	1.5	230/130	237/128	208/116	− 22/−14	206/112	− 2/− 4	12
J. N.	45 F	4	230/130	228/126	230/137	± 0/+ 7	216/132	−14/− 5	8
I. O.	58 F	9	164/100	166/ 88	177/ 93	+ 13/− 7	200/101	+23/+ 8	8
H. O.	55 F	4	260/160	253/140	236/135	− 24/−25	240/129	+ 4/− 6	8
M. P.	46 F	6	220/115	213/130	191/104	− 29/−11	206/113	+15/+ 9	6
M. R.	37 F	7	218/119	194/112	185/111	− 33/− 8	178/107	− 7/− 4	5
Y. R.	44 F	16	250/160	244/166	235/160	− 15/± 0	227/147	− 8/−13	7
A. R.	38 F	3	215/123	150/ 98	150/ 98	− 65/−25	158/102	+ 8/+ 4	5
F. Ro.	59 F	2	190/125	166/ 98	165/101	− 25/−24	155/ 94	−10/− 7	9
A. S.	70 F	10	200/110	180/ 98	164/ 89	− 36/−21	150/ 86	−14/− 3	7
L. Smk.	48 F	8	220/125	174/ 94	168/ 92	− 52/−33	169/ 99	+ 1/+ 7	4
H. S.	51 F	10	240/140	244/122	237/116	− 3/−24	197/102	−40/−14	9
E. S.	54 F	1	200/100	206/100	207/101	+ 7/+ 1	186/ 86	−21/−15	18
M. Su.	66 F	7	215/120	238/106	239/111	+ 24/− 9	167/ 86	−72/−25	15
M. T.	55 F	10	220/108	153/ 88	170/ 93	− 58/−15	157/ 84	−13/− 9	19
C. V.	52 F	5	230/140	144/ 84	178/100	− 52/−40	167/100	−11/± 0	16
An. Wa.	47 F	7	260/150	182/ 86	178/ 84	− 88/−66	158/ 84	−20/± 0	15
A. Wil.	54 F	12	270/150	230/120	235/125	− 35/−25	208/112	−17/−13	5
A. Win.	50 F	4	198/110	186/ 90	185/ 91	− 13/−19	163/ 86	−22/− 5	7
Average of 38 males	50.9	....	222/127	200/115	197/113	− 25/−14	192/113	− 5/± 0	9.3
Average of 48 females	49.5	....	230/130	204/113	201/111	− 29/−19	191/106	−10/− 5	9.4
Average of 86 patients	50.1	....	227/129	202/114	200/112	− 27/−17	192/109	− 8/− 3	9.3

in many individual patients despite the small difference in the means for the group as a whole. As might be anticipated, in most instances the readings on admission fell between the acceptance blood pressure levels and those representing the mean for the first week of hospitalization but there is wide variation between these limits and there are a number of exceptions to the general trend. Because of the many environmental factors influencing the blood pressure on the first day or two of hospitalization, even when basal levels are recorded, we have elected to use the mean of the

basal blood pressures obtained throughout the first week of hospitalization as the more statistically sound baseline. Similar considerations led us to employ the mean of the basal blood pressures of the last three weeks of hospitalization as our endpoint, rather than the mean for the last week alone.

−8/−3 mm. Hg. The major proportion of patients showed comparatively little change in basal blood pressure; as Table III indicates, the over-all change in basal systolic pressure was within ± 10 mm. Hg in forty instances, the over-all change in basal diastolic pressure was within ±5 mm. Hg in

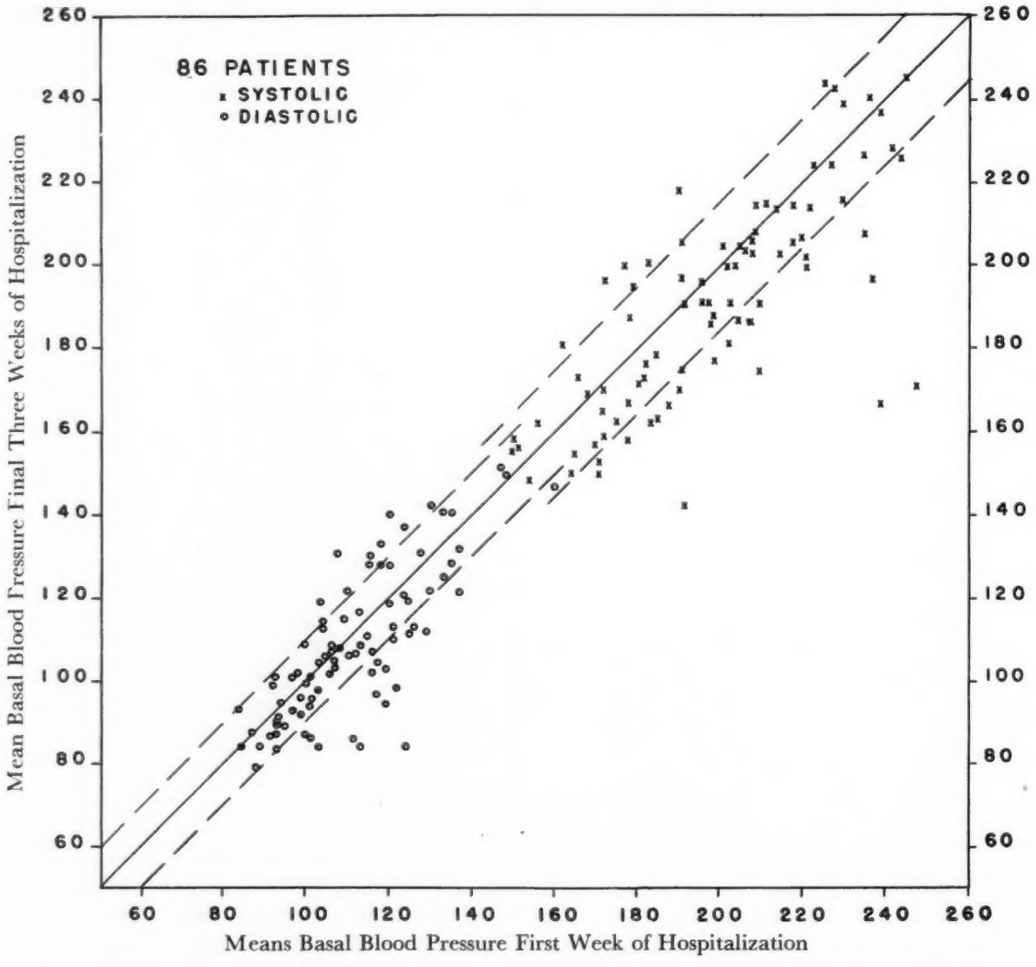

FIG. 1. Comparison of mean basal blood pressures in first week of hospitalization with mean basal blood pressures of last three weeks of hospitalization. Points falling above solid diagonal represent patients showing increases in basal blood pressure; points falling below represent decreases. The broken lines in the area of diastolic pressures (circles) indicate the limits ±10 mm. Hg; the broken lines in the area of systolic pressures (crosses) indicate the limits ±15 mm. Hg.

Comparison of mean basal blood pressures in the *first week* of hospitalization with the mean basal blood pressures obtained in the *last three weeks* of hospitalization on a standardized regular diet brings out several significant points. (Table II and Fig. 1.) The difference in the means of the two groups (200/112 and 192/109 mm. Hg, respectively) is conspicuously small, only thirty-nine instances, and only nine patients showed both a fall in basal systolic pressure greater than 20 mm. Hg and a fall in basal diastolic pressure greater than 10 mm. Hg.

This apparent over-all stability of our patient population was, of course, conditioned in part by the rigid initial selection of cases and by the use of basal blood pressure measurements made under standardized

conditions intended to minimize fluctuations due to environmental influences. It is therefore all the more significant, as more detailed examination of the data in Table II reveals, that the individual response to prolonged hospitalization was so variable in final basal blood pressure was 165/95 or less in nine instances.

In addition to the over-all *degree* of change in basal blood pressure which occurred between the first week and the last three weeks of hospitalization, the *rate* at which such

TABLE III

ANALYSIS OF CHANGES IN BASAL BLOOD PRESSURE ASSOCIATED WITH HOSPITALIZATION IN EIGHTY-SIX PATIENTS WITH ESSENTIAL HYPERTENSION

Change in Diastolic Pressure (mm. Hg)	Change in Systolic Pressure (mm. Hg)								Diastolic Group Totals
	> +20	+11 to +20	+1 to +10	0	−1 to −10	−11 to −20	−21 to −30	> −30	
> +20	.....	.....	.....	.....	.....	.....	.....	.....	.....
+11 to +20	1, 0 (1)*	3, 1 (4)	1, 1 (2)	.....	.....	.....	1, 0 (1)	.....	6, 2 (8)
+6 to +10	0, 1 (1)	2, 2 (4)	1, 1 (2)	.....	0, 2 (2)	2, 0 (2)	.....	.....	5, 6 (11)
+1 to +5	.....	.....	1, 3 (4)	.....	2, 4 (6)	1, 0 (1)	.....	.....	4, 7 (11)
0	.....	.....	1, 1 (2)	.....	1, 0 (1)	0, 2 (2)	.....	.....	2, 3 (5)
−1 to −5	.....	.....	1, 2 (3)	1, 0 (1)	4, 5 (9)	3, 4 (7)	0, 3 (3)	.....	9, 14 (23)
−6 to −10	.....	.....	0, 2 (2)	1, 0 (1)	1, 1 (2)	2, 2 (4)	2, 0 (2)	.....	6, 5 (11)
−11 to −20	.....	.....	.....	.....	1, 1 (2)	1, 2 (3)	2, 2 (4)	1, 2 (3)	5, 7 (12)
> −20	.....	.....	.....	.....	1, 0 (1)	0, 2 (2)	.....	0, 2 (2)	1, 4 (5)
Systolic group totals	1, 1 (2)	5, 3 (8)	5, 10 (15)	2, 0 (2)	10, 13 (23)	9, 12 (21)	5, 5 (10)	1, 4 (5)	38, 48 (86)

* First figure indicates number of males, second figure number of females, third figure in parentheses gives total number of patients in each category.

so many patients as to make prediction, on the basis of observations in the first week, extremely hazardous. As indicated in Table III, fifty-nine of the eighty-six patients showed a fall in basal systolic pressure which in fifteen instances exceeded −20 mm. Hg; whereas twenty-seven patients showed no change or a rise in basal systolic pressure which exceeded +20 mm. Hg in two instances. Of the fifty-one patients whose basal diastolic pressure fell, the fall in seventeen instances exceeded −10 mm. Hg; while thirty-five patients showed no change or a rise in basal diastolic pressure which exceeded +10 mm. Hg in eight instances. It should be noted (Table II) that as a result of hospitalization alone the basal diastolic pressure in twenty-three of these eighty-six patients fell to 95 mm. Hg or below, the basal systolic pressure in fourteen fell to 165 mm. Hg or below, and that the changes occurred was subjected to analysis. These data are of interest in regard to the duration of control observations required to attain a state of stabilization before initiating the experimental period of observation, whether on the rice diet or other forms of therapy. Here again there was marked and unpredictable variation in the response of individual patients. Figure 2 illustrates the more common variations in type and rate of change in weekly mean basal blood pressures observed. Case A. A. is representative of the largest single group of patients, namely, those who showed either no distinct change in blood pressure levels throughout the period of observation or only an insignificant decline. Case H. S. is representative of twelve patients who showed a gradual fall to stable levels. In general, when maximal falls exceeding 10 mm. Hg systolic or diastolic pressure occurred, the

peak response usually appeared after six weeks of hospitalization, so that unless the control period of hospitalization were sufficiently prolonged these responses would be attributed to the specific effects of therapy. In six patients, however, a marked and persistent fall in blood pressure occurred within the first three weeks of hospitalization (Case M. Su.). Case I. O. represents a group of sixteen patients whose blood pressure fluctuated up and down widely during the period of observation, stabilization never being achieved in some instances. Case A. Co. is illustrative of the few patients who showed a steady rise in both systolic and diastolic blood pressure.

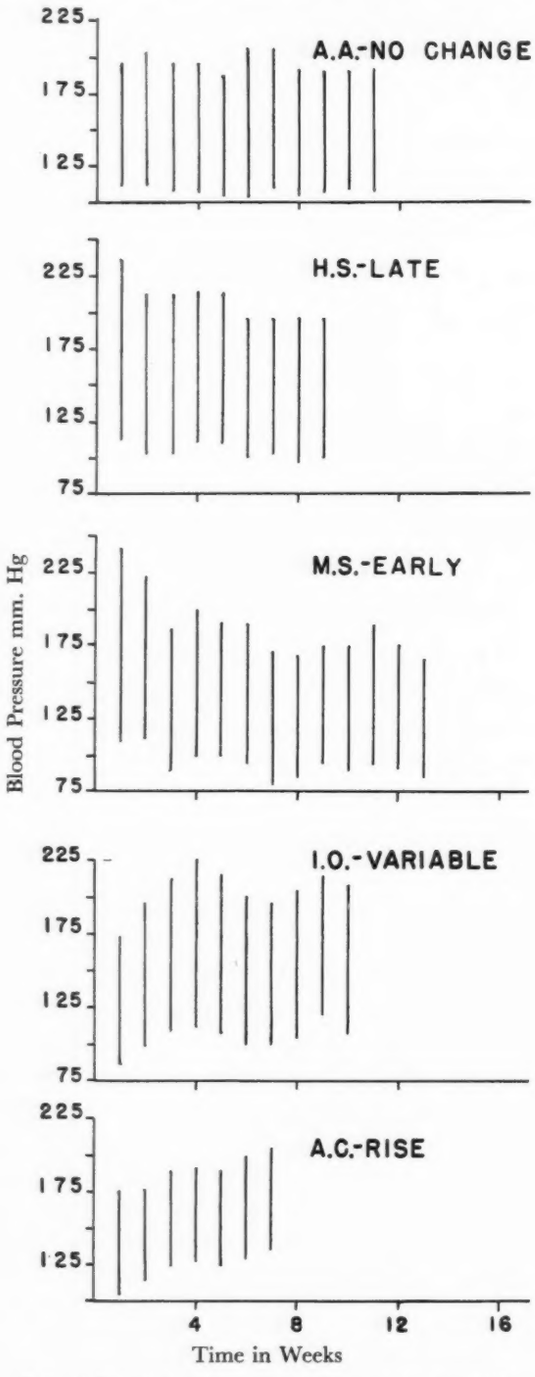

FIG. 2. Basal blood pressure response to hospitalization in five patients, illustrating the five more common variations encountered. The top of each bar indicates mean basal systolic pressure for one week, the bottom of each bar indicates mean basal diastolic pressure for that week.

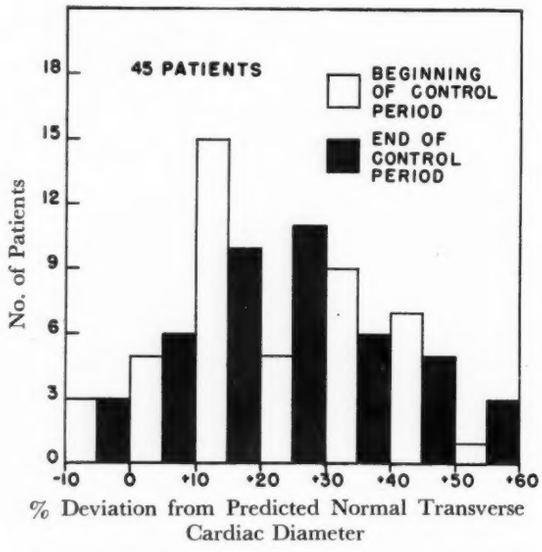

FIG. 3. Histogram representing frequency distribution of per cent deviation of measured from predicted (normal) transverse cardiac diameter in forty-five patients at the beginning and at the end of the period of hospitalization.

Heart Size. Satisfactory data on changes in heart size during the period of hospitalization are available in forty-five cases. Of these twenty were in congestive failure on admission and were receiving digitalis therapy which had to be continued throughout the period of observation in twelve instances but could be withdrawn in eight cases.

Figure 3 is a frequency-distribution curve indicating the per cent difference of the measured from the predicted transverse diameter of the cardiac silhouette at the beginning and at the end of the period of hospitalization on a standardized regular hospital diet. It will be noted that thirty-seven of the forty-five patients initially were

found to have cardiac transverse diameters more than 10 per cent above prediction based on patient height and weight and that after hospitalization this number was virtually unchanged (thirty-six patients). However, a reduction in heart size greater than 1 cm. was noted in five cases, the mean reduction in this group being 1.6 cm. (Table IV.) This was not associated with any significant fall in diastolic blood pressure, but may have been related to reduction in weight[4] in two obese patients who voluntarily restricted their diet, with restoration of compensation on digitalis in two patients, and with both factors in the fifth patient. The remaining forty patients showed no significant reduction in heart size during the period of observation although thirty-four had cardiac enlargement and twelve were markedly decompensated on admission to the hospital.

TABLE IV

EFFECT OF HOSPITALIZATION ON HEART SIZE

	Number of Patients				Mean Change in Heart Size (cm.)	Mean Period of Hospitalization (wk.)	Mean Change in Diastolic Pressure (mm. Hg)	Mean Weight Change (kg.)
	Total	With Enlarged Heart	Markedly Decompensated	On Digitalis				
Reduction > 1 cm.....	5	4	2	2	−1.6	11.4	−1.6	−5.4
Reduction < 1 cm.....	40	34	12	10	+0.13	8.3	−3.7	+0.1

TABLE V

CHANGES IN ELECTROCARDIOGRAMS OBSERVED DURING PROLONGED HOSPITALIZATION IN FORTY-ONE PATIENTS WITH ESSENTIAL HYPERTENSION

	Total Number Patients	Duration of Hospitalization (wk.)	Change in Basal Diastolic Pressure (mm. Hg)	Change in Heart Size (cm.)	Change in Body Weight (kg.)
Changes Toward Normal in ECG	6				
H. F., male, 53.....		8	− 4	−0.4	+ 2.8
T. F., female, 51.....		21	−16	−1.0	− 9.1
M. T., female, 55.....		18	−10	+0.1	+ 0.2
A. K., female, 34.....		17	− 4	−2.2	−11.3
M. Ba., female, 40.....		9	+ 1	+1.1	+ 1.4
M. P., female, 46.....		6	+11	−0.5	+ 0.2
		Means: 13.0	− 3.6	−0.5	− 2.6
No Change in ECG.....	35	Means: 7.3	− 4.9	−0.03	+ 0.2

Electrocardiograms. Canabal and Warneford-Thompson,[5] in a study of fifty hypertensive patients followed for eight years, noted progressive electrocardiographic changes in 50 per cent, no significant change in 40 per cent and spontaneous regression toward normal in 10 per cent of their patients. Improvement in the ECG occurred exclusively in women under the age of fifty and was usually minor in degree. Bechgaard[6] found regression toward normal in electrocardiograms in only 3 per cent of 264 hypertensive patients followed eleven years. Both these studies were conducted in clinic outpatients.

Table V summarizes our findings in the forty-one patients suitable for this study. Spontaneous changes toward normal, as indicated by tendency of inverted T waves to become upright and depressed S-T seg-

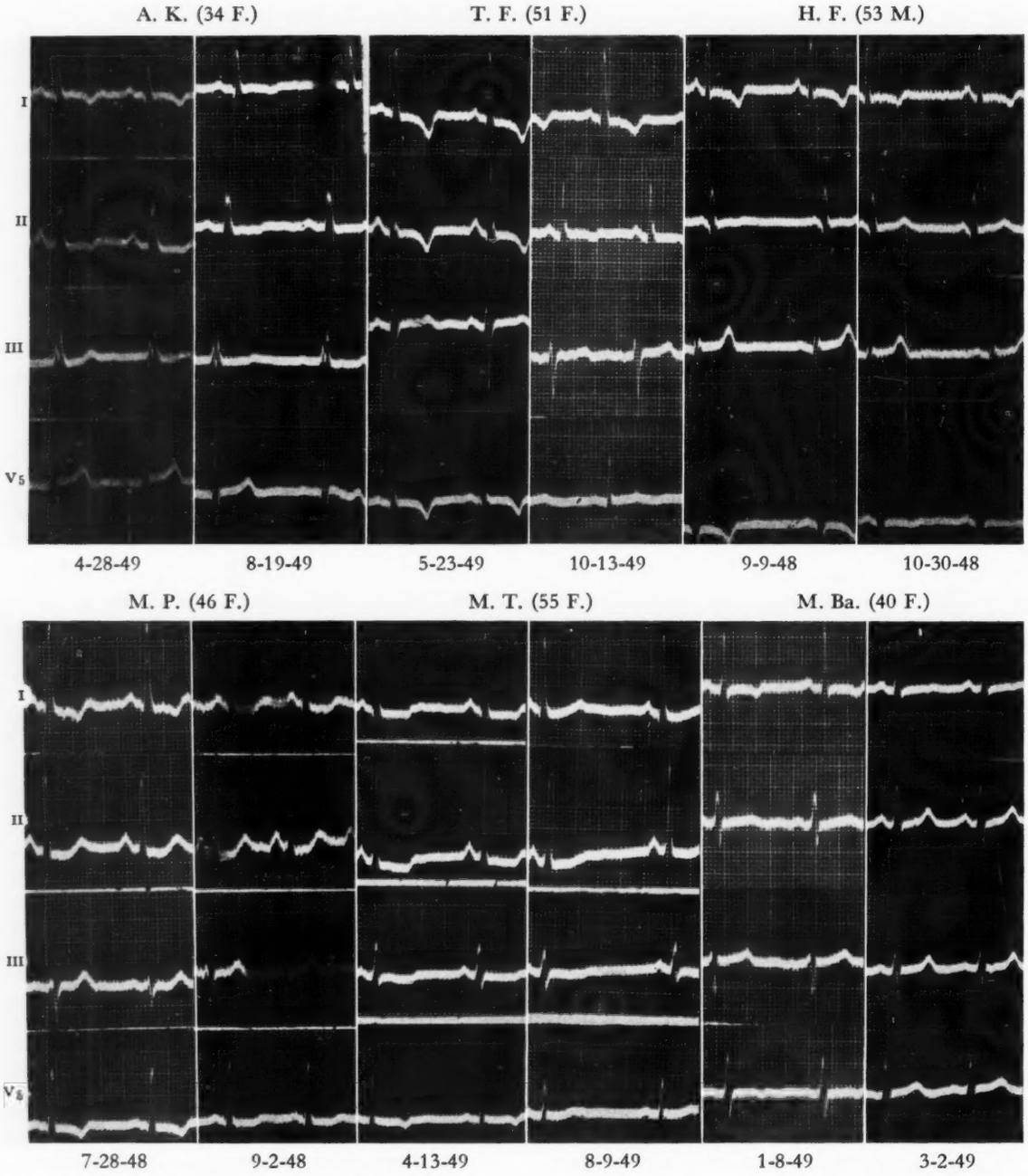

FIG. 4. Effect of hospitalization on the electrocardiograms of six patients. A. K.: T_1 and T_2 tended to become upright. T. F.: T_1 became less markedly inverted, T_2 tended to become upright, Tv_5 became upright. H. F.: T_1 and Tv_5 tended to become upright, T_2 more distinctly upright. M. P.: T_1 and Tv_5 changed from inverted to upright. M. T.: T_1, T_2, Tv_5 changed from inverted to upright. M. Ba.: T_1 and Tv_5 changed from inverted to upright, T_2 more definitely upright.

ments to become isoelectric, were observed in six patients (Fig. 4), five of whom were females. It will be noted (Table v) that there were no significant differences with respect to changes in basal diastolic blood pressure, heart size or body weight between the cases showing apparent improvement and those who did not. The mean duration of hospitalization, however, was greater in those patients with electrocardiographic changes toward normal. Whether this signifies that such changes might have occurred spontaneously over a prolonged period in any environment, or that the

hospital environment itself exerted some beneficial effect, cannot be ascertained.

Retinopathy. Table VI summarizes the eyeground changes observed over the period of hospitalization on a standard hospital diet (mean: 9 weeks) in forty-nine patients with Keith-Wagener grade II or more advanced retinopathy and in whom we have adequate descriptions or photographs. According to this system of classification, grade I–II refers to vessel caliber and related changes only; grade III includes superimposed exudates, hemorrhages, retinal edema or peripapillitis; grade IV is characterized by the presence of papilledema.

Five of the sixteen patients in grade II showed progression of vessel changes such as increased spasticity, pallor of vessel walls, crossing signs and sheathing of vessels and decrease in A-V ratio; in two of these patients one hemorrhage and one exudate appeared so that they were reclassified as grade III. Two patients appeared to show spontaneous improvement in A-V ratio, crossing signs and spasticity but remained in grade II.

Five of the twenty-three patients in grade III showed progressive worsening of vascular phenomena while under observation, one of these also developing increased numbers of exudates and hemorrhages, and two showing increased peripapillary edema not considered to warrant the designation of papilledema. Eight patients showed improvement in retinopathy, in two instances with disappearance of hemorrhages (reclassified as grade II), in four with regression of peripapillary edema and reduction in number but not disappearance of hemorrhages and exudates, and two with improvement in vessel changes associated with some reduction in hemorrhages and exudates.

Of the ten patients in grade IV, two showed spontaneous disappearance of papilledema and were reclassified in grade III; two others showed improvement, some reduction in papilledema in one instance and reduction in peripapillitis in the other. One patient showed definite worsening of retinopathy, with increased peripapillary edema, more numerous hemorrhages and progressive vessel changes.

In none of the cases exhibiting alterations in eye grounds during the period of hospitalization could a distinct correlation with changes in basal systolic or diastolic pressure be made out.

TABLE VI

CHANGES IN HYPERTENSIVE RETINOPATHY OBSERVED DURING PROLONGED HOSPITALIZATION IN FORTY-NINE PATIENTS WITH ESSENTIAL HYPERTENSION

Total Number Patients	Initial Keith-Wagener-Barker Grade	No Change	Worse	Improved	Final Keith-Wagener-Barker Grade
16	II	9	5	2	II (14 patients) III (2 patients)
23	III	10	5	8	II (2 patients) III (21 patients)
10	IV	5	1	4	III (2 patients) IV (8 patients)

Miscellaneous Laboratory Findings. No significant changes were noted in other laboratory data obtained during the course of hospitalization on a standardized regular hospital diet. Of interest, however, were the results of serum cholesterol and phospholipid determinations. The mean serum total cholesterol level was found to be higher by 33 mg. per cent than the mean of our control normotensive series. In addition, repeated determinations revealed that in two-thirds of the cases greater fluctuations in serum cholesterol levels occurred than are observed in normal subjects. The serum phospholipid content was found to bear the same close relationship to cholesterol level as reported by Albrink et al.[7] It would appear, therefore, that in respect to lipid metabolism patients with essential hypertension form a heterogeneous group which, as might be anticipated, includes a number of individuals with the characteristics of patients with coronary atherosclerosis.[8] Further details regarding these relationships in serum lipids and their implications will appear elsewhere since no evidence was obtained that prolonged hospitalization on a regular hospital diet had any significant influence on this aspect of essential hypertension.

COMMENT

It is generally recognized that the manifestations of essential hypertension, in particular blood pressure levels, are subject to wide spontaneous fluctuation[9,10] and that hospitalization *per se* is apt to give at least temporary benefit. It is also generally appreciated that precise data on these points are largely lacking but while this important deficiency has been much deplored little effort appears to have been made, at least with adequate organization and on a sufficiently large scale, to rectify the deficiency. The data recorded here are not sufficient to satisfy the general requirement since too few subjects have been studied and these few were too highly selected to give a representative cross section of the hypertensive population. It is significant, however, that these highly selected patients showed such extraordinary individual variation since they were deliberately chosen for manifestations of advanced essential hypertension of long duration and hence might be expected to show more stability and relatively less transient fluctuation. The need of further coordinated studies of this type in larger groups of hypertensive patients seems evident.

In analyzing our data no attempt was made to differentiate changes referable directly to the hospital environment from such spontaneous fluctuation in course as might have occurred over the same period of time in any environment, since such a dissociation obviously is impracticable.

The data presented emphasize clearly the necessity for a prolonged control period of hospitalization in the evaluation of any therapeutic program conducted on patients in a hospital environment. The variation in response to hospitalization *per se* is so great and so unpredictable in the individual patient that each subject must serve as his own control. Otherwise, valid appraisal of the specific effects of therapy would seem to be quite impossible.

SUMMARY

1. To provide baseline points of reference for evaluation of the results of allegedly specific treatment of essential hypertension in a hospital environment, a study was made of the effects of hospitalization *per se* in eighty-six patients observed for a mean period of nine weeks on a standardized regular diet.

2. Observations on changes in symptomatology, basal blood pressure, heart size, electrocardiographic findings and retinopathy are recorded.

3. Precise data are afforded to support the general impression that the response of individual patients with essential hypertension to hospitalization *per se* is so variable and unpredictable that a prolonged period of observation is a prerequisite to valid appraisal of the specific effects of therapy.

Acknowledgments: We are indebted to many for assistance and advice rendered in the course of this study. Special thanks are due to our ophthalmologic consultants, particularly Drs. Robert R. Chace and Howard E. Wiener; to Dr. Henry K. Taylor, radiologist; to the Misses Gwelda McPhee, Gertrude Chesin and Frances E. Godtfring for technical assistance; and to Miss Hannah Epstein, dietitian.

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Effects of Diet in Essential Hypertension*

II. Results with Unmodified Kempner Rice Diet in Fifty Hospitalized Patients

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RECENT reports by Kempner[1–4] describing impressive results obtained in the treatment of hypertensive cardiovascular disease by a stringent rice-fruit-sugar dietary regimen have reawakened interest in the use of low-sodium diets in hypertension.[5,6] As prescribed by Kempner, the rice diet consists of an average of 250–350 gm. rice (dry weight) daily to which white sugar or dextrose may be added ad libitum, also any kind of fruit juice or fruit except nuts, dates, avocadoes or any dried or canned fruit or fruit derivatives to which substances other than white sugar have been added. Fluid intake is restricted to 700–1,000 ml. per day in the form of fruit juices. This diet according to Kempner[3] contains, per 2,000 calories, not more than 5 gm. fat, about 20 gm. protein derived from rice and fruit, not more than 200 mg. chloride and 150 mg. sodium, and is devoid of cholesterol. Apart from a daily vitamin and iron supplement no medication is given unless specifically indicated. The strict rice diet is generally continued without modification for about 100 days or until the conditions which indicated its use have disappeared; small amounts of non-leguminous vegetables, potatoes, lean meat or fish, prepared without salt or fat, may then be added as modifications of the strict rice diet. Kempner[3] estimated that 322 (64.4 per cent) of 500 patients, most of whom were seriously ill and had failed to respond to other forms of treatment, were benefited by the rice diet as judged by one or more of the following objective criteria: decrease of at least 20 mm. Hg in "mean" arterial blood pressure (systolic + diastolic divided by 2); reduction in transverse diameter of the heart of 18 per cent or more; change in T_1 from inverted to upright; disappearance or marked improvement in severe retinopathy. Worthy of note was the response in blood pressure, since of the total of 500 patients (mean blood pressure before treatment 199/117 mm. Hg) 25 per cent showed a return to normal or almost normal levels (below 145/95 mm. Hg). Even more impressive was the regression of retinopathy, for example, complete disappearance of papilledema in twenty-three of eighty-eight patients and improvement in five of the remainder. A great many of the patients experienced relief from headache, giddiness, fatigue, dyspnea and substernal pain. Approximately one-third of the patients were not benefited by the rice diet, as judged by Kempner's criteria, after an average trial of about two months. There were twenty-six deaths while under treatment, all but one in patients with marked renal impairment.

Apart from the important clinical implications of this work, the rice diet is of quite extraordinary interest from the point

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of view of the nutritional requirements of man and the metabolic effects of restrictive diets on the bodily economy. As Kempner[4] has pointed out, "the rice diet contains less sodium and less chloride than any other diet which has been devised to reduce the sodium and chloride intake. It contains less protein than any other diet which has been devised to reduce the protein intake [and yet maintain, essentially, nitrogen equilibrium]. It contains less cholesterol and other fat [lipid] than any other diet which has been devised to reduce the cholesterol and fat intake." Kempner's metabolic data indicate that patients with hypertensive cardiovascular disease can make a remarkable adjustment to these restrictions and maintain caloric, nitrogen and electrolyte equilibrium for long periods on the unmodified rice regimen.

Despite the large scale and elaborate documentation of Kempner's work, however, the place of the rice diet in the management of hypertensive cardiovascular disease remains controversial. As pointed out in recent critical but eminently fair reviews,[5,7–9] Kempner's reports leave unassessed the role of a number of possible contributory factors, and there are other uncertainties.

(1) Since control periods of observation appear to have been inadequate in many if not most cases, the effects of spontaneous variations in course and the benefits of a favorable patient environment *per se* cannot be evaluated. Many of the patients in question had severe hypertensive disease of long standing and a considerable proportion presented serious late complications, but our own experience indicates[10] that even such subjects may show the most varied and unpredictable individual response to a hospital environment and general supportive measures. Our data[10] also make clear, however, that the over-all incidence of pronounced benefit obtained by Kempner with the rice diet far exceeds what can be ascribed solely to spontaneous variation or to the effects of hospitalization alone. (2) It is not possible to appraise the role of psychotherapeutic factors associated with the rice diet. Fanaticism, extravagant promises, threats and cajolement all have an important influence on therapy although it is not apparent how amelioration of retinopathy, cardiac enlargement, congestive failure, etc., can be accounted for in this way. These objective signs of improvement would seem to be unsusceptible to emotional bias in interpretation of results. (3) The validity of the reasoning which led Kempner from his initial manometric studies on kidney tissue to clinical application of the rice diet is highly problematic but this unsound origin should not prejudice appraisal of the empirical value of the rice diet in essential hypertension. However, the necessity for drastic reduction of protein intake, a reflection of Kempner's earlier preoccupations, is not yet established either on theoretic or empirical grounds, even though recent experiments do suggest that the protein content of the diet may influence the blood pressure in hypertensive rats.[11] The growing realization of the important role of sodium restriction[12–14] makes this uncertainty even more relevant. (4) It is not clear how much of the benefit derived from the rice diet should be attributed in some cases to relief of congestive failure and its associated phenomena by an unnecessarily onerous form of salt restriction, and how much if any represents amelioration of the underlying hypertensive disorder. (5) The diet is unpalatable, monotonous and difficult to maintain long enough to exert its effects. As Kempner himself has emphasized[4] it is ineffective and, indeed, dangerous unless there is continuous supervision and constant check of the blood and urine. In fact, the rice diet makes such demands on both patient and doctor that except in relatively few instances it would seem to be an impracticable form of sustained therapy for hypertension. (6) Finally, studies of the rice diet by other investigators[13–20] have given conflicting results which leave the efficaciousness of the diet in hypertension still in doubt. Some of these studies were carried out in outpatient clinics and hence cannot be directly compared with Kempner's work. Others are indecisive because too few patients were studied, preliminary control periods were insufficient for orientation, the period on the rice diet was too short, or evidence is wanting that sufficiently rigid restriction of salt was maintained; it is doubtful that the rice diet can be continuously prepared sufficiently free of salt in general hospital kitchens serving other foods.

Page and Corcoran[8] conclude in connection with the use of the rice diet in hypertension that

"at present, it is not possible on the basis of published evidence to arrive at any considered opinion of its value." This appraisal is equally cogent in relation to other low-salt diets in current use in the treatment of hypertension.

The present report incorporates the results of a two-year trial of the rice diet, under controlled hospital conditions, in fifty patients with essential hypertension. The letter of the strict Kempner regimen was adhered to even in those items without apparent rationale.

The design of the investigation was that of a metabolic experiment comprising: (1) An adequate fore-period on a standardized regular hospital diet. The control period was continued as long as was necessary to stabilize blood pressure levels (mean duration:10.1 weeks). Those patients who failed to attain reasonably steady levels or whose blood pressure fell to equivocal levels of hypertension were discharged from the study. (2) An adequate period on the Kempner rice regimen. The unmodified rice diet was continued as long as indicated to judge its effects or until interruption was necessitated either by the patients' refusal to continue or by some untoward complication. The mean duration of the rice diet period in the fifty patients was 10.5 weeks. (3) An adequate period on the rice diet modified by the systematic addition of salt, protein or fat to determine what is and is not essential in the Kempner regimen and how far the diet may be diversified without losing its benefits. The effects of modifications of the strict rice diet are still under study and will be reported in greater detail in a subsequent communication.

MATERIAL AND METHODS

Selection of Patients. As indicated in our introductory baseline study of the effects of hospitalization *per se* in eighty-six patients with essential hypertension,[10] 105 patients with marked hypertension were admitted to this Service for the rice diet program in the period July, 1948 to March, 1950. These patients were recruited from a total of approximately 900 patients interviewed and examined at various New York City hospitals and clinics. Preference was given throughout to the most severe cases of essential hypertension available to us, patients with marked hypertension (minimal acceptable blood pressure 220/120 mm. Hg with the exception of six patients presenting other features of interest), manifestations of rapidly progressive hypertensive disease and complications of the advanced stages of hypertensive cardiovascular disease. In so doing it was our intention to give the rice diet a really rigorous trial; moreover, as Kempner has pointed out, the rice regimen should be reserved only for the more severe cases of hypertension and after all forms of more conservative management have proved unavailing. The patients admitted agreed to remain in the hospital four to six months for the combined control and rice diet periods.

The present series of fifty patients (twenty-eight males, twenty-two females) was culled from the eighty-six cases previously described.[10] Of the thirty-six patients excluded, in eleven instances blood pressure levels had fallen to normal limits, or virtually so, during the control period on a regular diet. Ten patients signed out and three died during the control period, an additional patient dying of cerebrovascular accident in the initial weeks of the rice diet period. Four very obese patients were used to study the effects of weight reduction diets. In the seven remaining cases observations on the rice diet had not been continued long enough at the time of this writing to warrant inclusion in the present series.

The medical background of the fifty patients forming the subject of this report is indicated by the following tabulation of major complications recorded in various hospitals and clinics prior to and upon admission to this Service:

	No. of Patients
Abnormal electrocardiogram*	27
Myocardial infarction	3
Advanced retinopathy	25
Keith-Wagener-Barker grade III	18
Keith-Wagener-Barker grade IV	7
Congestive failure	29
Cerebrovascular accidents	13
Hypertensive encephalopathy	2
Marked renal insufficiency (BUN > 50 mg. %)	2

* In eighteen additional patients digitalis effects made interpretation difficult.

Standardization of Patient Activity, Medication and Diet. Upon admission the patients were confined to bed, with lavatory privileges, for the first three weeks of the control period; if their condition then permitted ambulation, they were

allowed up for the remainder of the control period and throughout the rice diet period, participation in occupational therapy and ward recreational activities being encouraged. Medications such as digitalis, mercurial diuretics and sedatives were discontinued or reduced whenever possible. The weight was recorded daily.

The diet employed in the control period contained approximately 2,200 calories and was of the following composition:[10] protein 80 gm., fat 85 gm., carbohydrate 275 gm., sodium chloride 10 gm. (mean of 173 mEq. sodium by flame photometer analyses), cholesterol 1.0 gm., fluids 2,500 ml.

In the rice diet period the daily caloric intake was 1,800 to 2,400 calories (adjusted to individual requirements) and of the following composition: protein about 29 gm.,* fat less than 3 gm., carbohydrate 420–570 gm., sodium 2.5 to 7 mEq., potassium 73.5 mEq. (mean figure), calcium 13 mEq., phosphorus 15 mEq., cholesterol 0.0 gm., fluids limited to 1,000 ml. fruit juices. In addition each patient received daily 1 feosol® tablet (0.2 gm. ferrous sulfate); 1 vi-penta perle forte®† containing vitamin A 5,000 U.S.P. units, thiamine hydrochloride 3 mg., riboflavin 3 mg., pyridoxine hydrochloride 1 mg., calcium pantothenate 3 mg., niacinamide 20 mg., ascorbic acid 75 mg., vitamin D 1,000 U.S.P. units, vitamin E acetate 1 mg.; and a placebo capsule containing 1 gm. sucrose which could be replaced by salt when desired without knowledge of the patient. The daily allotment of rice was 300 gm., dry weight, supplying approximately 1,050 calories, with white sugar, fresh or sodium-free preserved fruits and fruit juices providing an additional 1,000 or more calories. When weight loss was appreciable, extra calories were given in the form of dextrose and condensed fruit syrups.

The patients received five feedings daily: Three main meals consisting of steamed rice (100 gm. each meal) with three fruits or juices; and two supplementary feedings of fruit or fruit juices, one in mid-afternoon and one at bedtime. Such variety as was possible was afforded in the fruits and juices, of which ten different kinds were served each day with attention to color and attractiveness of the tray and to individual likes and dislikes. Addition of assorted fruit juice sherbets, rice-fruit puddings, fruit-flavored hard candies, etc., helped to break the monotony of the diet. Because of the presence of peptic ulcer symptoms in five patients when the rice diet was instituted and reactivation of ulcer symptoms on the unmodified rice diet in 10 additional patients, in these instances the rice was ground and given with a low-sodium powdered milk preparation, lonalac,®,* in cereal form, fruits were cooked and puréed and all fruit juices were replaced by sodium-free water.

It should be noted that the rice diet as employed by us contains more protein than stated by Kempner. This discrepancy probably arises from our use of a Texas-grown, long-grain American Patna–type rice which was selected after preliminary Kjeldahl analyses of ten different varieties of rice disclosed marked differences in nitrogen content. The following values, expressed in gm. % N, were obtained: 0.85 and 0.95 (pearl), 1.03, 1.12, 1.20 (glutinous), 1.20, 1.22 (long-grain), 1.42 (brown), 1.45 (Texas-grown, long-grain American Patna). The sodium content of all varieties was found to be extremely low, hardly measurable by flame photometry.

Many of our patients began the rice diet and more continued it with considerable reluctance. It was therefore necessary to bolster morale by explaining the purpose of the regimen and by reporting encouraging details of improvement as they developed. In general, however, overt psychotherapy was held at the minimum level possible even if it could not be wholly excluded. As a further check on the role of unavoidable psychotherapy and related subjective factors, the investigation was so designed that salt in capsule form could be added to the diet, unknown to the patient, either when the rice diet was initiated or after a good response was obtained.

Control of Sodium Intake on the Rice Diet. The rice diet was prepared in a special diet kitchen installed for the sole purpose and operated by a full-time cook-kitchen aid team supervised by a full-time dietitian. Aliquots of the diet were checked for sodium content by flame photometry from time to time and found to remain within low limits of 2.5 to 7 mEq. A source of contamination with sodium was found at one period to be the tap water employed for steaming the

* Daily N intake 4.9 gm. (mean of analysis of 20 diets) of which 4.35 gm. was rice protein N. Using the conventional factor of 6.25 this is equivalent to more than 30.6 gm. protein. According to Jones[21] the conversion factor for rice protein should be 5.95, which is equivalent to 29 gm. protein.

† We are greatly indebted to Hoffmann-LaRoche, Inc., for a generous supply of these vitamin capsules.

* Mead Johnson and Co. kindly supplied large quantities of lonalac® for this study.

rice and dish-washing—the sodium content of the water, which usually was negligible, rose in a period of marked depletion of the New York City reservoirs. To overcome this it was necessary to install a cation-exchange column for removal of sodium.

Constant check of the patients for advertent or inadvertent contamination of the diet with salt was found to be essential. The urines were tested for chloride daily or every other day.

Hospital Work-up. Routine work-up of each patient was made in the control period and various tests were repeated as indicated at regular intervals in the control and rice periods. The routine work-up included detailed history and physical examination, basal blood pressures, funduscopy,[10] heart size in 2-meter films,[10] electrocardiograms,[10] gastrointestinal x-ray series, basal metabolism, venous pressure, circulation time, amytal floor and cold pressor tests, erythrocyte sedimentation rate, hematologic examination, urinalyses, PSP excretion, urea clearance, serum urea N or NPN, fasting blood sugar, glucose tolerance, serum cholesterol and cholesterol esters, phospholipids and neutral fat, total proteins, albumin and globulins (Howe method), sodium and potassium (by internal standard flame photometer), carbon dioxide content, calcium and phosphorus. When indicated, such additional examinations as eye-ground photography, benzodioxane test, BSP test (5 mg./kg. body weight), thymol turbidity,[22] cephalin flocculation[23] and "dicumarol tolerance" tests were performed.

In addition a number of special studies were made in connection with points of particular interest. These included renal function studies of glomerular filtration rate (inulin), renal plasma flow (PAH) and Tm_{PAH}, estimation of plasma volume (T-1824 dye space), thiocyanate space, antipyrine space, nitrogen and electrolyte balance studies, and cardiac output measurements by cardiac catheterization with calculation of peripheral vascular resistance before and after the rice diet.

Method of Taking and Recording Blood Pressure. Blood pressure measurements were made by assigned physicians and nurses with a mercury sphygmomanometer three times weekly in each patient before rising in the morning. Six successive readings at approximately thirty-second intervals were made. The lowest systolic and the lowest diastolic pressure reading of the six obtained was recorded as the basal pressure for that day. The three basal systolic and diastolic pressures for each week were averaged, recorded as the mean basal pressures for that week and used for further analysis in both the control and rice diet periods.

Basal blood pressure levels are not, of course, representative of the patient's blood pressures throughout the day. For purposes of standardization, however, basal blood pressure levels are most likely to exclude pressor responses associated with the act of recording the blood pressure, as well as other extraneous psychologic and environmental factors during both the control and rice diet periods.

Special Laboratory Procedures Employed. T-1824 dye space and thiocyanate space were usually determined together by the simultaneous method of Gregersen and Stewart,[24] adapted to photoelectric colorimetry. Standard doses were employed. The usual precautions against hemolysis of blood samples were observed. The results were derived from ten- and sixty-minute arterial blood samples, without use of extrapolation technics.

Antipyrine space measurements were made by the method of Soberman et al.[25]

Renal function studies were carried out by constant-infusion clearance technics with the patient in the postabsorptive state. Urine collections were made with indwelling catheter, the bladder being washed with distilled water at the end of each clearance period. Femoral artery blood samples were obtained at the mid-point of each period, using heparin as anticoagulant. Inulin clearance was used as a measure of glomerular filtrate rate, inulin being determined by the method of Harrison[26] in Somogyi zinc filtrates of yeasted plasma and in diluted urine. Renal plasma blood flow was estimated by para-aminohippurate clearance. In the estimation of maximal tubular excretory capacity for para-aminohippurate (Tm_{PAH}) sufficiently high PAH plasma levels were maintained to ensure adequate tubular PAH loads.

A dicumarol tolerance liver function test was devised because of the observation of marked over-reaction of the prothrombin time in one of our patients on the rice diet when dicumarol was given. In this test the prothrombin time was determined, using the Link-Shapiro modification of Quick's method, and 300 mg. dicumarol was then given orally in a single dose. Another prothrombin time was obtained forty-eight hours later. No prolongation of prothrombin time was observed after forty-eight hours in hypertensive patients while on the control diet.

For estimation of serum lipids all bloods were drawn before breakfast. Free and total serum cholesterol levels were determined by the method of Schoenheimer and Sperry.[27,28] Duplicate analyses run in separate batches indicated average reproducibility within 1.5 per cent. In our hands the Schoenheimer-Sperry method has given values 0–40 per cent lower than levels obtained in the same sera by the Bloor method. Lipid phosphorus was determined in alcohol-ether filtrates of serum by the modification of Kendall and Davidson, phosphorus being measured by the method of Fiske and Subbarow. Duplicate analyses of lipid phosphorus were reproducible within 1 per cent. Total lipids were estimated gravimetrically upon an aliquot of the petroleum ether extract obtained after extracting the serum with Bloor's 3:1 alcohol-ether mixture and evaporating the solution to dryness. Serum neutral fat was approximated by subtracting from the weight of total lipids the sum of the amounts of phospholipids, total cholesterol and the fatty acids present in the cholesterol ester fraction (0.7 × weight of cholesterol in the esters).

For the nitrogen and electrolyte balance studies patients were segregated in private ward rooms with special facilities. Food consumed during the studies was prepared and weighed separately in the rice diet kitchen. An amount of food equivalent to that consumed by the patient was saved daily for analysis. Each metabolic period was of seven days' duration. At the end of each one-week period aliquots of the daily diets were combined, mixed, samples obtained for analysis and ashed by the method of Toscani and Buniak.[29] Aliquots of the daily urine output and the daily fecal specimens for one week were similarly combined, mixed and samples taken for analysis. Nitrogen was determined by the macro-Kjeldahl technic. Flame photometry was employed for sodium and potassium analyses.

RESULTS

Symptomatology. A summary of the clinical history and prior therapy, clinical status at the beginning and end of the control period, and again at the end of the rice diet period is given for each of our patients in Table I. For comparison of the incidence of changes in presenting complaints during the control period (mean duration: 10.1 weeks) and rice diet period (mean duration: 10.5 weeks) the data are analyzed in Table II.

Control period: A substantial proportion of our patients improved symptomatically during the control period, the incidence of improvement varying from approximately 20 to 35 per cent in different categories. (Table II.) The most consistent benefit derived was in respect to manifestations of congestive failure, roughly one-third of the patients with cardiac decompensation showing distinct improvement. Severe, often incapacitating headaches proved more refractory, about one-fifth of the patients who exhibited this symptom obtaining relief. Four patients with impaired vision as a presenting complaint failed to improve. The number of virtually asymptomatic patients increased from four to nine.

Rice diet: Those patients who showed amelioration of symptoms during the control period generally sustained their improvement throughout the rice diet period, frequently in the face of reduction or discontinuance of previously required medications such as digitalis. In addition, marked improvement occurred in many patients who were not benefited during the control period. (Tables I and II.) This was most striking in respect to decreased intensity and frequency of severe and hitherto refractory headaches, disappearance of peripheral edema, amelioration of exertional dyspnea and orthopnea, and improved vision. There was remission of hypertensive encephalopathy in the two patients who presented this complication. The incidence and maintenance of improvement in these categories (Table II) was distinctly greater than could be anticipated on the basis of spontaneous variations in course or the use of general supportive measures.[10]

Nine patients failed to improve symptomatically on the rice diet. One patient (Case F. B.) developed electrocardiographic evidence of a coronary occlusion, with marked transitory fall in blood pressure, in the eighth week on the rice diet. Case T. Mc. showed progressive deterioration on the rice diet and died in uremia; another

TABLE I

CLINICAL STATUS OF FIFTY PATIENTS WITH ESSENTIAL HYPERTENSION BEFORE AND AFTER CONTROL AND RICE DIET PERIODS

Patient	Age and Sex	Known Duration of Hypertension (yr.)	Past History	Previous Therapy	Control Period			Rice Period		
					Clinical Status on Admission	Change in Clinical Status	Duration (wk.)	Change in Clinical Status	Weight Change (kg.)	Duration (wk.)
A. A.	65 M	2	Headaches, dizziness 2 yr.	Sedation, hospitalization	Dizziness, headaches	No change	15	No headaches, dizziness. Weakness and fatigue on diet but tolerated diet well	−2.5	5
C. A.	58 M	10	Headaches and syncope 10 yr., exertional dyspnea 7 yr., dizziness 2 yr., epistaxis 1 yr.	Digitalis, hospitalization, sedation	Headaches, dizziness, dyspnea, nocturnal cough, edema	Relief of headaches, dyspnea, dizziness, less edema	11	Loss of nocturnal cough, edema, tolerated diet fairly well	−3.3	7
Mu. C.	57 M	3	Mild diabetes 15 yr., hypertension 3 yr., progressive loss of vision 1.5 yr., "heart attack" 1 yr. ago, exertional dyspnea 1 yr., headaches 8 mo.	10 units PZI, sedation, digitalis,† bed rest	Progressive loss of vision, grade III retinopathy, headaches, BUN 38 mg. %	No change; digitalis cut, BUN 32 mg. %	12	Improvement in vision, loss of headaches, diet well tolerated	−1.9	12
*H. Col.	47 M	5	Headaches, numbness in legs 5 yr., pulmonary edema 1 yr. ago, coarctation aorta diagnosed, 2 strokes past year	Sedation, 5 hospital admissions, digitalis,† mercurials	Palpitations, vertigo, dyspnea on exertion	No change; digitalis continued	8	No relief of complaints; epigastric distress, weakness, somnolence on diet, digitalis continued	−1.7	13
R. C.	48 M	11	Dyspnea 1 yr., orthopnea, pulmonary edema, exertional dyspnea 4 mo.	Bed rest, hospitalization, digitalis,† mercurials	Exertional dyspnea, orthopnea	Progressive dyspnea and edema after digitalis cut	7	Relief of exertional dyspnea, orthopnea, edema, diet well tolerated	−0.2	9
A. Co.	46 M	½	Headaches 3 yr., nausea, vomiting 1 mo., exertional dyspnea, blurring of vision 1–2 mo.	Hospitalization	Intense occipital headaches, nausea and vomiting; BUN 32 mg. %, grade IV retinopathy	Increase in headaches, nausea, vomiting, attack of hypertensive encephalopathy, BUN 51 mg. %	4	Loss of headaches, relief of symptoms, weakness on diet but tolerated it	−8.0	10
S. D.	52 M	13	3 strokes past 1½ yr.	Hospitalization	Left hemiplegia and dysarthria, grade III retinopathy	No change	9	No change, became very belligerent on diet	−2.2	10
A. D.	44 M	2	Severe occipital headaches	Demerol, morphine, bed rest	Occipital headaches	No change	9	Loss of headaches, tolerated diet well	−2.9	8
H. F.	53 M	4	Headaches 4 yr., "heart attack" 2 yr. ago, dizziness 1½ yr., angina 6 mo.	Sedation, bed rest, nitroglycerine	Headaches, dizziness, angina, grade III retinopathy	No change	13	Relief of headaches, angina; dizziness persists, developed epigastric distress, tolerated diet poorly	−4.8	14
R. G.	53 M	4	Headaches 4 yr., exertional dyspnea, ankle edema 4 mo.	Reduction diet, digitalis,† mercurials, bed rest, low NaCl diet	No complaints; grade III retinopathy	No change; digitalis cut	8	No change; tolerated diet well	−6.5	14
F. H.	49 M	5	Headaches 1 yr., fatigability 1 yr.	Hospitalization, sedation	Headaches	No change	6	Loss of headaches, tolerated diet well until 24th wk. then developed epigastric distress and quit diet	−5.8	16
C. H.	40 M	7	Dizziness, headaches for 7 yr., left hemiplegia 2½ yr. ago	3 hospitalizations, sedation, physiotherapy	Headaches	Relief of headaches, asymptomatic	16	Developed epigastric distress, stools guaiac positive, duodenal ulcer by x-ray, diet discontinued	−0.9	10
W. H.	59 M	20	Exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, ankle edema 1 yr.	Hospitalization	No complaints; slight edema, BUN 32 mg. %, grade III retinopathy	No change	11	Tolerated diet well	−1.6	9

* Lonalac supplement to basic rice diet. † Digitalis continued to date of admission.

TABLE I (*Continued*)

Patient	Age and Sex	Known Duration of Hypertension (yr.)	Past History	Previous Therapy	Control Period			Rice Period		
					Clinical Status on Admission	Change in Clinical Status	Duration (wk.)	Change in Clinical Status	Weight Change (kg.)	Duration (wk.)
P. K.	59 M	1	Headaches, dyspnea, chest pains	None	Headaches, mild exertional dyspnea	Relief of headaches and dyspnea, asymptomatic	20	Tolerated diet well	−2.3	12
G. K.	48 M	?	Exertional dyspnea 1 yr., ankle edema, paroxysmal nocturnal dyspnea 4 mo. ago	Hospitalization, mercurials, digitalis†	Dyspnea, orthopnea, edema, BUN 53 mg. %, grade III retinopathy	No change; BUN 98 mg. %; digitalis continued	7	Dyspnea improved, digitalis continued, weakness, fatigue and hunger on diet; tolerated diet poorly	−4.1	6
C. La.	54 M	1½	Pulmonary edema 1½ yr. ago, frequent paroxysmal nocturnal dyspnea, diminution of vision 4 mo. ago, mild diabetes 1 yr. ago	Bed rest, mercurials, digitalis,† hospitalization	Chest pain, dyspnea, grade III retinopathy, BUN 59 mg. %	Required frequent treatment for bouts of pulmonary edema, digitalis continued, BUN 73 mg. %	8	Digitalis continued, relief of dyspnea, paroxysmal nocturnal dyspnea and pulmonary edema, developed marked weakness, anemia, requiring transfusion, tolerated diet poorly	−2.7	6
S. La.	60 M	2	Epistaxis 4 yr. ago, sudden onset paroxysmal nocturnal dyspnea followed by exertional dyspnea, orthopnea for past 2 yr.	Digitalis,† hospitalizations, mercurials, oxygen	Dyspnea at rest	No change; digitalis continued	6	Digitalis continued, no dyspnea, tolerated diet well	−2.4	5
B. L.	60 M	2	Ankle swelling, headaches and exertional dyspnea 1½ yr.	Digitalis,† mercurials, low-salt diet	Edema, exertional dyspnea, headaches, papilledema	No change; digitalis continued	12	Loss of ankle edema, less dyspneic, diminished headaches, tolerated diet well	−2.0	14
T. Mc.	46 M	3	Epistaxis, paroxysmal nocturnal dyspnea, exertional dyspnea, edema of 6 mo. duration	Sedation, diuretics, digitalis,† hospitalization	Dyspnea, paroxysmal nocturnal dyspnea, edema, grade III retinopathy	No change; digitalis continued	6	No relief of dyspnea, weakness, occasional nausea and vomiting, tolerated diet fairly well; died in uremia	−1.8	12
F. M.	40 M	¼	Exertional dyspnea 3 mo.	Hospitalization, sedation	Exertional dyspnea, marked edema, headaches, grade III retinopathy	Dyspnea at rest, disorientation, headaches	3	Loss of exertional dyspnea, cleared sensorium, fewer headaches, tolerated diet well	−8.3	9
S. N.	52 M	10	Hemiplegia 2 yr. ago	Digitalis, low-salt diet, ammonium chloride	Edema, orthopnea, dyspnea	Loss of dyspnea and ankle edema	6	No change; tolerated diet well	−3.0	16
B. P.	41 M	19	Headaches 10 yr., exertional dyspnea 2 yr., right hemiplegia 4 mo. ago	Sedation, hospitalization	Right-sided paralysis, headaches, grade III retinopathy	No change	13	Relief of headaches, developed tenesmus, otherwise tolerated diet well	−3.6	17
*E. R.	61 M	15	Myocardial infarctions 6 and 7 yr. ago, left hemiplegia 1 yr. ago, duodenal ulcer 10 yr.	Sympathectomy, rice diet	Grade III retinopathy	No change	10	No change; tolerated diet well	−1.5	3
G. R.	54 M	5	Exertional dyspnea, ankle edema, blurring of vision 8 mo.	Hospitalization, digitalis†	Slight edema, dyspnea, blurred vision, papilledema	Dyspnea at rest following digitalis withdrawal; redigitalized, no complaints	10	Occasional gastrointestinal upset, tolerated diet well	−5.5	5
C. Ro.	49 M	7	Several strokes, left visual field defect, dysarthria for 2 yr., quadriplegia 3 mo.	Hospitalization, rice diet	Impaired speech, locomotion, vision	No change	11	No change, tolerated diet well	−1.7	16
F. Ru.	40 M	1	Ankle edema, dyspnea 7 yr. ago, stroke 1 yr. ago	Bed rest, sedation, low-salt diet	Left hemiplegia, headaches	No change	14	Complained of weakness, constipation, no change in symptomatology, tolerated diet poorly	−2.1	5

* Lonalac supplement to basic rice diet. † Digitalis continued to date of admission.

TABLE 1 (*Continued*)

Patient	Age and Sex	Known Duration of Hypertension (yr.)	Past History	Previous Therapy	Control Period			Rice Period		
					Clinical Status on Admission	Change in Clinical Status	Duration (wk.)	Change in Clinical Status	Weight Change (kg.)	Duration (wk.)
F. Sm.	64 M	7	Dyspnea, ankle edema 7 yr.	Hospitalization	No complaints; BUN 32 mg. %	No change	15	Occasional dizziness on standing, tolerated diet well	+1.0	13
S. S.	45 M	8	Headaches 8 yr., weakness, easy fatigability 3 yr., exertional dyspnea 2 yr.	Rest, sedation, rice diet	Easy fatigability, grade III retinopathy, BUN 33 mg. %	No change	7	Constipation, no change in symptomatology, tolerated diet poorly	−1.7	8
M. Ba.	40 F	4	Headaches, aphasia 1 yr. ago, blurred vision 9 mo. ago, right hemiplegia 3 yr. ago	Low-salt diet, rice diet, hospitalization	Paresthesias, blurred vision, headaches, dizziness	No change	9	Disappearance of headaches, dizziness, blurred vision, tolerated diet well	+1.5	17
F. B.	55 F	2½	Ankle edema 5 yr., headaches 2½ yr. ago, exertional dyspnea and orthopnea 2½ yr., precordial pain 1 yr.	Weight reduction, sedation, hospitalization	Headaches and dizziness, exertional dyspnea, precordial discomfort	Asymptomatic, depressed	7	Silent coronary 8th rice diet week, weakness, leg pains, agitation and depression, weight loss on diet, tolerated diet poorly	−9.0	7
M. Be.	57 F	14	Palpitations, dyspnea, precordial pains 15 yr.; 2 bouts hypertensive encephalopathy past 2 yr.	Sedation, hospitalization, salt-poor diet	Weakness, headaches, palpitation	Asymptomatic	9	Tolerated diet well save for weakness, developed mild anemia	−1.6	5
D. B.	38 F	2	Vertigo, syncope 2 yr.	Salt-poor diet, sedation	Headaches, occasional vertigo	Decreased frequency and severity of headaches	7	Palpitations, no change in headaches, indigestion, epigastric distress	−0.4	7
J. Cl.	50 F	10	Headaches, scotomas, exertional dyspnea, right hemiplegia, orthopnea, ankle edema past 4 yr.	Low-salt diet, diuretics, digitalis	Headaches, exertional dyspnea, orthopnea, grade III retinopathy	No change, digitalis withdrawn	12	Relief from headaches and dyspnea, weight gain, tolerated diet well	+1.3	11
*Ma. C.	61 F	9	Diabetes 10 yr., exertional dyspnea 2 yr., paroxysmal nocturnal dyspnea, substernal pain, ankle edema	Digitalis	Paresthesias left side, blurred vision, dizziness, headaches, glycosuria	Athetosis, left side, glycosuria diminished	13	Epigastric pain, gastric ulcer discovered, relief from modified rice diet, loss of headaches, diminished athetosis, tolerated diet well	−1.4	33
J. Co.	32 F	1½	Headaches 1½ yr., tinnitus 1½ yr., blurred vision 5 mo., dyspnea and palpitation 4 mo., orthopnea 3 mo., ankle edema 1 mo., paroxysmal nocturnal dyspnea 3 wk., dizziness 3 wk., puffiness of the face 1 mo.	None	Headaches, palpitation, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ankle edema	Asymptomatic, except for occasional nausea, vomiting, diarrhea, amenorrhea	8	Weakness, tolerated diet poorly	−1.6	7
C. D.	42 F	17	Pre-eclampsia 17 yr. ago, dyspnea, orthopnea and ankle edema 1 mo., nausea, vomiting, abdominal pain; weight loss 20 pounds 1 yr.	Hospitalization, diuretics, digitalis†	Dyspnea, edema, epigastric pains, anorexia, nausea and vomiting for 2 wk., failing vision, papilledema; BUN 39 mg. %	Digitalis continued, recompensated, no abdominal pain, nausea or vomiting, vision unimproved, BUN 36 mg. %	8	Improved visual acuity, digitalis cut after 8th week	−2.6	10
D. K.	48 F	7	Ankle edema 4 yr. ago exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea 4 yr.	Digitalis,† mercurials, low-salt diet and hospitalization	Exertional dyspnea, orthopnea, palpitation	Disappearance of orthopnea, no change in other symptoms, digitalis withdrawn	7	Relief of exertional dyspnea, attack of transient left-sided weakness, tolerated diet fairly well	−2.7	10
M. Ki.	54 F	16	Hypertension noted with pregnancy, headaches, dizziness, tinnitus, palpitations 5 yr., weakness 1 yr., rapid pulse 6 mo.	Sterilization, sedation	Rapid pulse and weakness 6 mo., grade III retinopathy	Transient aphasia, paroxysmal auricular tachycardia, headaches	8	None, fatigability on diet, tolerated diet well	−1.6	10

* Lonalac supplement to basic rice diet. † Digitalis continued to date of admission.

TABLE I (*Continued*)

Patient	Age and Sex	Known Duration of Hypertension (yr.)	Past History	Previous Therapy	Control Period			Rice Period		
					Clinical Status on Admission	Change in Clinical Status	Duration (wk.)	Change in Clinical Status	Weight Change (kg.)	Duration (wk.)
*M. Kn.	57 F	30	Precordial pain, exertional dyspnea, paroxysmal nocturnal dyspnea, ankle edema, possible stroke over past 10 yr.	Digitalis,† nitroglycerine, salt-poor diet, diuretics	Dyspnea on exertion, headaches, dizziness	Digitalis withdrawn, no dyspnea, other symptoms unchanged, epigastric distress, x-ray diagnosis of duodenal ulcer	12	Modified rice diet tolerated well, loss of headaches	−5.1	9
S. Lau.	26 F	5	Headaches 3 yr., ankle edema 8 mo., attack paroxysmal nocturnal dyspnea 2 wk. ago	Digitalis, rice diet, reduction diet	Edema, occasional headaches, tachycardia, grade III retinopathy	No change	15	Disappearance of ankle edema and tachycardia, tolerated diet well except for some weakness	−4.2	12
E. M.	70 F	4	Exertional dyspnea, dizziness, headaches, insomnia 4 yr. ago, paroxysmal nocturnal dyspnea, ankle edema past 3 yr.	Low-sodium diet, digitalis,† mercurials	Exertional dyspnea, orthopnea, marked edema, grade III retinopathy	Digitalis continued, peripheral edema, rales in lungs diminished	13	Relief of exertional dyspnea, edema, digitalis cut, tolerated diet well	−4.9	11
A. Mo.	40 F	4	Paroxysmal nocturnal dyspnea, transient loss of vision 8 mo. ago, attack of syncope 6 mo. ago	Bilateral sympathectomy 1 yr. ago	Mental confusion, nausea, transient episodes of blindness, headaches, dizziness, grade III retinopathy	Disappearance of symptoms save for episodes of blindness, dizziness, headaches	8	No relief of symptoms, tolerated diet well	−3.0	12
I. Mu.	48 F	1½	Headaches, exertional dyspnea, weakness 1½ yr.	Reduction diet, rice diet	Left hemiplegia, headaches	No change	12	Reduction in frequency of headaches, tolerated diet well	−0.9	11
N.	45 F	4	Ulcerative colitis 4 yr., dyspnea, edema, orthopnea 4 yr., epistaxis 2 yr.	Salt-free diets, mercurials, digitalis,† 7–8 hospitalizations	Abdominal pains, dyspnea, edema, papilledema	No change, digitalis continued	8	No change in bowel complaints, digitalis withdrawn, severe weakness, free of dyspnea, tolerated diet poorly	−5.6	12
H. O.	52 F	4	Stroke 2 yr. ago, headaches 6 mo., bouts of encephalopathy and unconsciousness 4 mo.; dyspnea on exertion, weight loss	2 previous hospitalizations	Headaches, nausea, vomiting, grade III retinopathy	Continuous headaches, 2 bouts of hypertensive encephalopathy, nausea, vomiting	8	Relief of headaches, nausea, encephalopathy, became agitated and paranoid requiring psychiatric care, tolerated diet fairly well	+5.0	19
Y. R.	44 F	16	Weakness, fatigue, dizziness 14 yr., hypertension, acute pulmonary edema 6 yr. ago, stroke 6 mo. ago	Partial thyroidectomy, cesarean section, mercurials, digitalis, sympathectomy, rice diet	Left hemiplegia and headaches, papilledema	No change, ambulated in wheel chair	7	Marked lethargy, tolerated diet poorly, weakness; died of stroke		9
H. S.	51 F	10	Headaches, dyspnea on exertion, ankle edema 10 yr., orthopnea and paroxysmal nocturnal dyspnea past 2 yr.	Digitalis,† phenobarbital, mercurials	Headaches, dyspnea, orthopnea, papilledema	Digitalis cut, slight edema in legs and few pulmonary rales noted	9	Lungs clear, headaches relieved, tolerated diet poorly	−2.8	7
M. Su.	66 F	7	Tinnitus, vertigo 7 yr.	Sedation, hospitalization	Dizziness and tinnitus	No change	15	No change, complained of weakness on diet	+1.0	7
C. V.	52 F	5	3–4 strokes past 1½ yr.	Hospitalized 3 times	Dysarthria, difficulty in walking	No change	16	No change, tolerated diet well	−1.4	16
An. Wa.	47 F	7	Coronary 3 yr. ago followed by exertional dyspnea and angina, paroxysmal nocturnal dyspnea 1½ yr. ago., ankle edema past 1 yr.	Hospitalized twice, bed rest, digitalis,† mercurials	Weakness, irritability, orthopnea, exertional dyspnea	Less orthopnea and exertional dyspnea, digitalis withdrawn	15	No change, developed epigastric distress, tolerated diet fairly well after modification with Lonalace	−0.3	8

* Lonalac supplement to basic rice diet. † Digitalis continued to date of admission.

patient (Case Y. R.) suffered a stroke after nine weeks on the rice diet and died within twenty-four hours—the only deaths in this group of fifty patients while on the rice diet in the hospital.

A number of minor but difficultly manageable complaints developed in the course of the rice period. There was, of course, general unhappiness about the stringent deprivations of the strict rice regimen. Many patients protested bitterly about anorexia and indeed revulsion with respect to the diet, at the same time complaining of unsated hunger. Emotional disturbances of the type associated with semi-starvation diets were frequent despite the usually insignificant weight loss. Lassitude and weakness were often pronounced, becoming a presenting complaint in fifteen patients as the more serious evidences of their underlying disease regressed on the rice diet. (Table II.)

The most serious complication encountered, however, and quite unexpectedly, was activation of obsolescent peptic ulcers apparently due to the acid fruit-juices, roughage and perhaps low protein content of the rice diet. Four patients presented complaints referable to peptic ulcer at the beginning and end of the control period, the rice diet therefore being modified from the start in the manner already indicated to avoid exacerbation of symptoms. Ten patients required similar modifications during the course of the rice diet due to development of gastrointestinal complaints. All but two of these were able to continue the modified diet without further significant distress. We have found it necessary to inquire diligently into the past history for forgotten indications of ulcer and also to carry out roentgenographic gastrointestinal studies routinely. All questionable patients are now placed from the start on a modification of the rice diet substituting sodium-free water for fruit juices and incorporating the

TABLE II

INCIDENCE OF CHANGES IN PRESENTING SYMPTOMS OF FIFTY PATIENTS WITH ESSENTIAL HYPERTENSION DURING CONTROL PERIOD (MEAN DURATION: 10.1 WEEKS) AND AFTER RICE DIET (MEAN DURATION: 10.5 WEEKS)

Symptom	Control Period				Rice Diet		Improved			
	First Week		Last Week		Last Week		Control		Rice	
	No. Cases	% of 50	No. Cases	% of 50	No. Cases	% of 50	No. Cases	%	No. Cases	%
Severe headaches	27	54	22	44	8	16	5	19	14	64
Dyspnea on exertion	20	40	13	26	5	10	7	35	8	62
Orthopnea	11	22	7	14	4	8	4	36	3	43
Dizziness	10	20	7	14	5	10	3	30	2	29
Edema	6	12	4	8	0	0	2	33	4	100
Heart consciousness	5	10	4	8	2	4	1	20	2	50
Paralysis from cerebrovascular accident	10	20	10	20	11	22				
Failing vision	4	8	4	8	2	4	0	0	2	50
Nausea, vomiting	4	8	2	4	0	0				
Hypertensive encephalopathy	2	4	2	4	0	0	0	0	2	100
Weakness, lassitude	3	6	3	6	15	30				
Peptic ulcer symptoms	4	8	4	8	2*	4				
Asymptomatic	4†	8	9†	18	21†	42				

* In these two patients peptic ulcer symptoms persisted in spite of modification of the rice diet; in all, five patients required modification of the rice diet to control symptoms from the start; ten more required modification during the rice diet. † Minor complaints are excluded.

use of lonalac® and rice ground in a mill to make a cereal, with all fruits cooked or puréed.

We did not encounter clinical manifestations unequivocally referable to the low-salt syndrome in this series of patients, even during the hot summer months, unless the weakness be ascribed to low salt intake. This is in contrast to our experience in chronic glomerulonephritis with severe renal damage, which has been almost uniformly bad as a result of salt loss in the urine.

Blood Pressure. In Table III are recorded our data on basal blood pressures at four periods of observation in each of the fifty patients with essential hypertension treated with the rice diet. The *acceptance blood pressures* are the lowest systolic and the lowest diastolic of the four to six readings made by one of us in various hospitals and clinics when examining the patient for acceptance to this Service, the patient being at rest in the recumbent position. The *first control pressure* is the mean of the basal blood pressures obtained during the first week of the control period of hospitalization on a standardized regular hospital diet; this figure serves as a baseline for analysis of the effects of hospitalization *per se*. The *final control pressure* is the mean of the basal blood pressures obtained during the last three weeks of the control period of hospitalization on the regular hospital diet; this figure gives the end point of the effects of hospitalization *per se* and also serves as the baseline for analysis of the effects of the rice diet. The *final rice diet pressure* is the mean of the basal blood pressures obtained during the last three weeks on the rice diet and is taken as the end point for the rice diet. The duration of the control period (mean: 10.1 weeks) and of the rice diet period (mean: 10.5 weeks) is indicated for each patient.

Striking differences were observed between *acceptance blood pressures* (mean: 227/132 mm. Hg) and those obtained in the *first control week* (mean: 205/115 mm. Hg). The difference between these means is −22/−17 mm. Hg, a figure which, though indicating a marked general decline, does not adequately reflect the quite remarkable falls observed in individual patients (for example Cases B. L., E. R., An. Wa., Table III). It should be noted in this connection that the fifty patients included in this series had been screened several times for persistence of hypertension and that the most striking examples of spontaneous falls in blood pressure should therefore have been excluded. Clearly, in evaluating the effects of the rice diet it would be fallacious in our patients to use as control figures the blood pressure readings recorded elsewhere, even by our own personnel, or the levels obtained in the first day or two following admission to the Service.[10]

Control period (Table III): Comparison of the over-all mean of the basal blood pressures in the *first week of the control period* (205/115 mm. Hg) with that of the over-all mean of the *final three weeks of the control period* (196/112 mm. Hg) indicates an insignificant over-all decline (−9/−3 mm. Hg). While a number of individual patients did show appreciable falls in basal systolic or diastolic pressure in the control period (Cases B. P., H. S. and M. Su., Table III), in twenty-six instances the change in basal systolic was within ± 10 mm. Hg, it was within ± 5 mm. Hg diastolic in twenty-five instances, and only four patients showed both a fall in basal systolic pressure greater than 20 mm. Hg and a fall in basal diastolic pressure greater than 10 mm. Hg. Only in Case An. Wa. was the basal blood pressure at the end of the control period less than 165/95 mm. Hg. Of course, these strikingly small changes reflect our selection of cases for the rice diet, as patients whose blood pressure did respond in the control period were not placed on the rice regimen except in a few instances of special interest in other respects.

Rice diet (Table III): Comparison of the over-all mean of the basal blood pressures of the *final three weeks of the control period* (196/112 mm. Hg) with that of the over-all mean of the *final three weeks on the rice diet* (167/96 mm. Hg) indicates a mean over-all decline of −29/−16 mm. Hg on the rice diet. Figures 1 and 2 bring out more clearly the difference in response of the blood pressure by contrasting the number of pa-

TABLE III

BASAL BLOOD PRESSURES IN FIFTY PATIENTS WITH ESSENTIAL HYPERTENSION IN CONTROL AND RICE DIET PERIODS

Patient	Age and Sex	Known Duration of Hypertension (yr.)	B.P. on Acceptance (mm. Hg)	Control Period				Rice Period		
				Mean Basal Blood Pressure			Duration (wk.)	Mean Basal Blood Pressure		Duration (wk.)
				First Week (*a*) (mm. Hg)	Last Three Weeks (*b*) (mm. Hg)	Δ *a* − *b* (mm. Hg)		Last Three Weeks (*c*) (mm. Hg)	Δ *b* − *c* (mm. Hg)	
A. A.	65 M	2	210/115	196/113	196/109	± 0/− 4	15	178/ 97	−18/−12	5
C. A.	58 M	10	220/120	197/107	191/105	− 6/− 2	11	145/ 85	−46/−20	7
Mu. C.	57 M	3	204/100	199/ 99	188/ 96	−11/− 3	12	156/ 89	−32/− 7	12
*H. Col.	47 M	5	214/114	222/111	214/111	− 8/± 0	8	200/101	−14/−10	13
R. C.	48 M	11	204/148	203/119	181/113	−22/− 6	7	180/107	− 1/− 6	9
A. Co.	46 M	0.5	230/160	190/130	218/142	+28/+12	4	211/135	− 7/− 7	10
S. D.	52 M	13	254/148	209/118	215/133	+ 6/+15	9	204/122	−11/−11	10
A. D.	44 M	2	190/125	191/116	170/107	−21/− 9	9	137/ 90	−33/−17	8
H. F.	53 M	4	240/120	196/ 93	191/ 90	− 5/− 3	13	132/ 76	−59/−14	14
R. G.	53 M	4	240/130	220/113	207/117	−13/+ 4	8	181/ 91	−26/−26	14
F. H.	49 M	5	230/110	209/112	208/107	− 1/− 5	6	159/ 92	−49/−15	16
C. H.	40 M	7	180/120	175/121	163/113	−12/− 8	16	133/ 96	−30/−17	10
W. H.	59 M	20	185/105	215/107	203/104	−12/− 3	11	202/ 97	− 1/− 7	9
P. K.	59 M	1	175/111	171/117	150/ 97	−21/−20	20	117/ 84	−33/−13	12
G. K.	48 M	?	220/120	244/118	226/128	−18/+10	7	183/103	−43/−25	6
C. La.	54 M	1½	230/120	201/ 97	205/ 93	+ 4/− 4	8	150/ 71	−55/−22	6
S. La.	60 M	2	180/130	182/117	176/105	− 6/−12	6	159/102	−17/− 3	5
B. L.	60 M	2	320/150	218/113	215/ 94	− 3/−19	12	177/ 84	−38/−10	14
T. Mc.	46 M	3	230/140	221/120	200/140	−21/+20	6	196/122	− 4/−18	12
F. M.	40 M	¼	250/150	214/148	214/150	± 0/+ 2	3	136/ 84	−78/−66	9
S. N.	52 M	10	225/145	210/126	191/113	−19/−13	6	135/ 94	−56/−19	16
B. P.	41 M	19	240/130	210/129	174/112	−36/−17	13	152/107	−22/− 5	17
*E. R.	61 M	15	255/160	172/102	170/ 96	− 2/− 6	10	146/ 84	−24/−12	3
G. R.	54 M	5	210/140	205/130	205/121	± 0/− 9	10	197/110	− 8/−11	5
C. Ro.	49 M	7	225/122	183/100	201/109	+18/+ 9	11	185/ 98	−16/−11	16
F. Ru.	40 M	1	220/120	181/124	172/121	− 9/− 3	14	175/123	+ 3/+ 2	5
F. Sm.	64 M	7	240/110	204/ 97	200/101	− 4/+ 4	15	144/ 78	−56/−23	13
S. S.	45 M	8	206/126	208/128	207/131	− 1/+ 3	7	183/123	−24/− 8	8
M. Ba.	40 F	4	240/160	227/147	224/152	− 3/+ 5	9	195/141	−29/−11	17
F. B.	55 F	2½	210/104	191/104	197/105	+ 6/+ 1	7	161/ 86	−36/−19	7
M. Be.	57 F	14	222/130	171/122	153/ 99	−18/−23	9	113/ 83	−40/−16	5
D. B.	38 F	2	190/120	154/ 94	148/ 95	− 6/+ 1	7	134/ 89	−14/− 6	7
J. Cl.	50 F	10	220/110	202/103	200/ 98	− 2/− 5	12	149/ 73	−51/−25	11
*Ma. C.	61 F	9	230/130	223/ 99	224/ 96	+ 1/− 3	13	191/ 86	−33/−10	33
J. Co.	32 F	1½	228/150	184/115	162/111	−22/− 4	8	121/ 84	−41/−27	7
C. D.	42 F	17	230/150	228/116	243/129	+15/+13	8	185/ 96	−58/−33	10
D. K.	48 F	7	220/130	159/100	165/109	+ 6/+ 9	7	135/ 89	−30/−20	10
M. Ki.	54 F	16	290/150	239/133	237/125	− 2/− 8	8	208/109	−29/−16	10
*M. Kn.	57 F	30	220/130	215/ 93	187/ 92	−28/− 1	12	143/ 67	−44/−25	9
S. Lau.	26 F	5	250/140	230/124	239/137	+ 9/+13	15	202/112	−37/−25	12
E. M.	70 F	4	240/120	203/ 94	191/ 89	−12/− 5	13	143/ 61	−48/−28	11
A. Mo.	40 F	4	210/140	219/130	206/122	−13/− 8	8	201/114	− 5/−/8	12
I. Mu.	48 F	1½	230/130	208/116	206/112	− 2/− 4	12	169/ 97	−37/−15	11
J. N.	45 F	4	230/130	230/137	216/132	−14/− 5	8	194/106	−22/−26	12
H. O.	52 F	4	260/160	236/135	240/129	+ 4/− 6	8	201/104	−39/−25	19
Y. R.	44 F	16	250/160	235/160	227/147	− 8/−13	7	231/140	+ 4/− 7	9
H. S.	51 F	10	240/140	237/116	197/102	−40/−14	9	159/ 87	−38/−15	7
M. Su.	66 F	7	215/120	239/111	167/ 86	−72/−25	15	168/ 84	+ 1/− 2	7
C. V.	52 F	5	230/140	178/100	167/100	−11/± 0	16	156/ 93	−11/− 7	16
An. Wa.	47 F	7	260/150	178/ 84	158/ 84	−20/± 0	15	163/ 86	+ 5/+ 2	8
Mean, males:			222/128	202/115	195/113	− 7/− 2	9.9	166/ 98	−29/−15	9.8
Mean, females:			233/136	209/115	198/112	−11/− 3	10.3	169/ 95	−29/−17	11.4
Mean of all cases:			227/132	205/115	196/112	− 9/− 3	10.1	167/ 96	−29/−16	10.5

* Lonalac supplement to basic rice diet.

FIG. 1. BLOOD PRESSURE CHANGES DURING CONTROL PERIOD

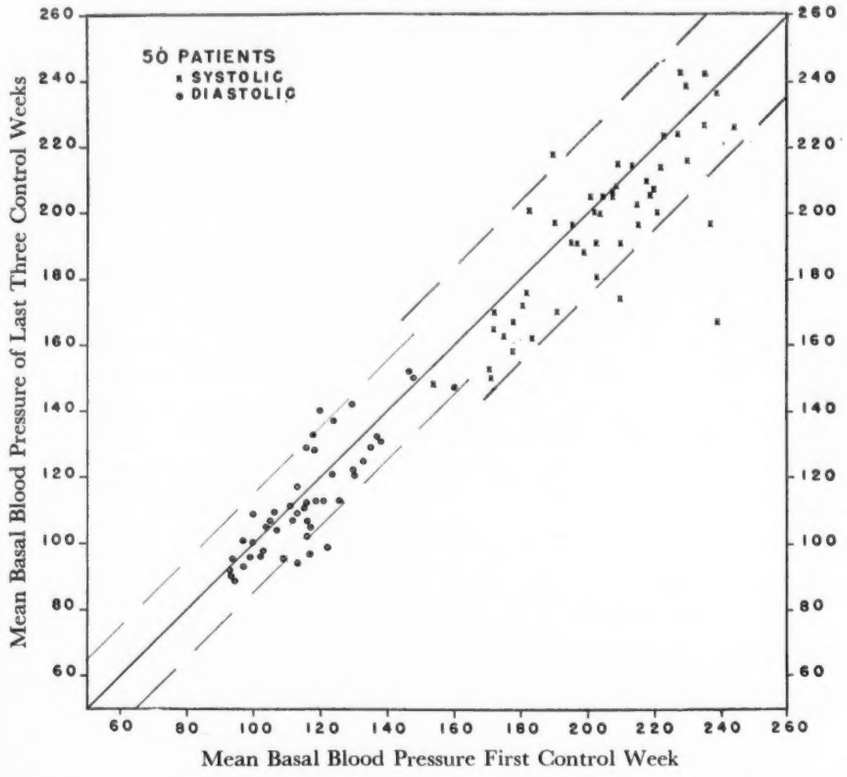

FIG. 2. BLOOD PRESSURE CHANGES DURING RICE DIET THERAPY

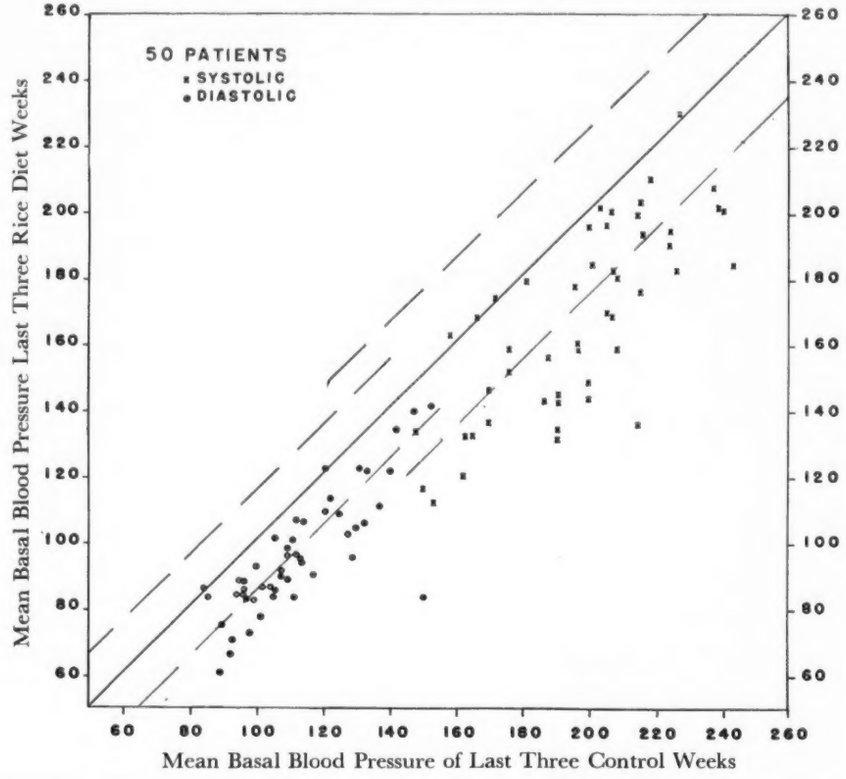

FIG. 1. Comparison of mean basal blood pressures in the first control week with mean of basal blood pressures of last three weeks of control period. Points falling above solid diagonal represent patients showing increases in basal blood pressure in the control period; points falling below represent decreases in the control period. The broken lines in the area of diastolic pressures (circles) indicate the limits ±15 mm. Hg; the broken lines in the area of systolic pressures (crosses) indicate the limits ±25 mm. Hg.

FIG. 2. Comparison of mean of basal blood pressures of last three weeks of control period with mean of basal blood pressures of last three weeks on rice diet. Points falling above solid diagonal represent patients showing increases in basal blood pressure in the rice diet period; points falling below represent decreases in basal blood pressure in the rice diet period (cf. Fig. 1). The broken lines in the area of diastolic pressures (circles) indicate the limits ±15 mm. Hg; the broken lines in the area of systolic pressures (crosses) indicate the limits ±25 mm. Hg.

tients who showed falls in basal systolic blood pressure greater than 25 mm. Hg (three and twenty-nine in the control and rice diet periods, respectively) or falls in the basal diastolic blood pressure greater than 15 mm. Hg (three and twenty-six, respectively). Further analysis of the effects of the rice diet on basal blood pressure (Table IV) discloses additional points of interest. The basal systolic pressure fell in forty-six of the fifty patients, the decline being 30 mm. Hg or more in twenty-six instances and exceeding 50 mm. Hg in seven instances. The basal diastolic pressure fell in forty-eight patients, the decline exceeding 20 mm. Hg in thirteen cases. In twenty-three cases the basal systolic pressure fell to 160 mm. Hg or below, in twenty-six instances the basal diastolic pressure fell to 95 mm. Hg or less. The final blood pressure on the rice diet was less than 160/95 mm. Hg in twenty patients.

TABLE IV

ANALYSIS OF CHANGES IN BASAL BLOOD PRESSURE IN CONTROL AND RICE DIET PERIODS IN FIFTY PATIENTS WITH ESSENTIAL HYPERTENSION*

Change in Diastolic Pressure (mm. Hg)	Change in Systolic Pressure (mm. Hg)									Diastolic Group Totals
	+11 to +20	+1 to +10	0	−1 to −10	−11 to −20	−21 to −30	−31 to −40	−41 to −50	> −50	
+11 to +20	2, *0*	2, *0*				1, *0*				5, *0*
+ 6 to +10	1, *0*	1, *0*								2, *0*
+ 1 to + 5		1, *2*	1, *0*	4, *0*	1, *0*					7, *2*
0				1, *0*	2, *0*					3, *0*
− 1 to − 5		2, *1*	1, *0*	6, *0*	4, *1*	2, *1*				15, *3*
− 6 to −10		1, *1*	1, *0*	2, *4*	3, *3*	2, *1*	0, *3*			9, *12*
−11 to −20				3, *2*	1, *3*	1, *5*	2, *6*	0, *2*	0, *2*	7, *20*
−21 to −30					1, *0*	0, *2*	0, *2*	0, *4*	1, *3*	2, *11*
> −30									0, *2*	0, *2*
Systolic Group Totals	3, *0*	7, *4*	3, *0*	16, *6*	12, *7*	6, *9*	2, *11*	0, *6*	1, *7*	50, *50*

* First figure is number of patients showing indicated changes in blood pressure in control period; second figure, in italics, is number of patients showing indicated changes in blood pressure in rice diet period.

Comparison of the magnitude of fall in blood pressure observed in our series of patients on the rice diet with that reported by Kempner[3] is illuminating. Kempner's mean pretreatment level in 500 patients was 199/117 mm. Hg, this series 196/112; the mean decline in systolic pressure was 36.5 mm. Hg, this series 29.0; 96 per cent of his patients showed some fall in diastolic pressure, this series 96 per cent; the mean decline in diastolic pressure was 16.7 mm. Hg, this series 16.0; the blood pressure fell below 145/95 in 25 per cent of cases, this series 24 per cent. The fact that our pretreatment levels represent those obtained after a long control period of hospitalization would tend, if anything, to make our responses to the rice diet more striking. In interpreting our results, however, we have not employed Kempner's criterion of improvement,[3] a decrease of 20 mm. Hg in "mean" arterial pressure (systolic plus diastolic pressure divided by 2), since the result may be overweighted by declines in high systolic pressure which may have little meaning, particularly without a sufficiently prolonged period of stabilization. In the absence of any satisfactory standards, we have not attempted evaluation of the observed responses in blood pressure to the rice diet in terms of clinical significance.

In addition to the over-all *degree* of change in basal blood pressure occurring on the rice diet, the *rate* of such changes was subjected to analysis. Figure 3 illustrates the more common variations in type and rate of change observed in the weekly mean basal blood pressures on the rice diet. Case F. Ru. is representative of six patients

who failed to show any response, Case A. A. illustrates the unsatisfactory response of eight additional patients whose blood pressure dropped less than 20 mm. Hg systolic and 10 diastolic. In Case A. Co., one of three such instances, there was a marked early fall in both systolic and diastolic pressure but this proved transitory and both soon reverted to the control levels. The more satisfactory course of the remaining thirty-three patients (66 per cent of our series) is illustrated in the next three examples. Case S. N. is representative of sixteen patients showing a gradual progressive decline in both systolic and diastolic basal pressures, usually with lessening of the pulse pressure. In this group a maximal response was attained only after six weeks on the rice diet. Cases F. M. and M. Be. illustrate the early fall in both systolic and diastolic basal pressure, again usually with smaller pulse pressures, observed in seventeen patients and sustained so long as the rice diet was continued. In this group less than six weeks on the rice diet, occasionally less than three weeks, were required to effect a maximal response in blood pressure.

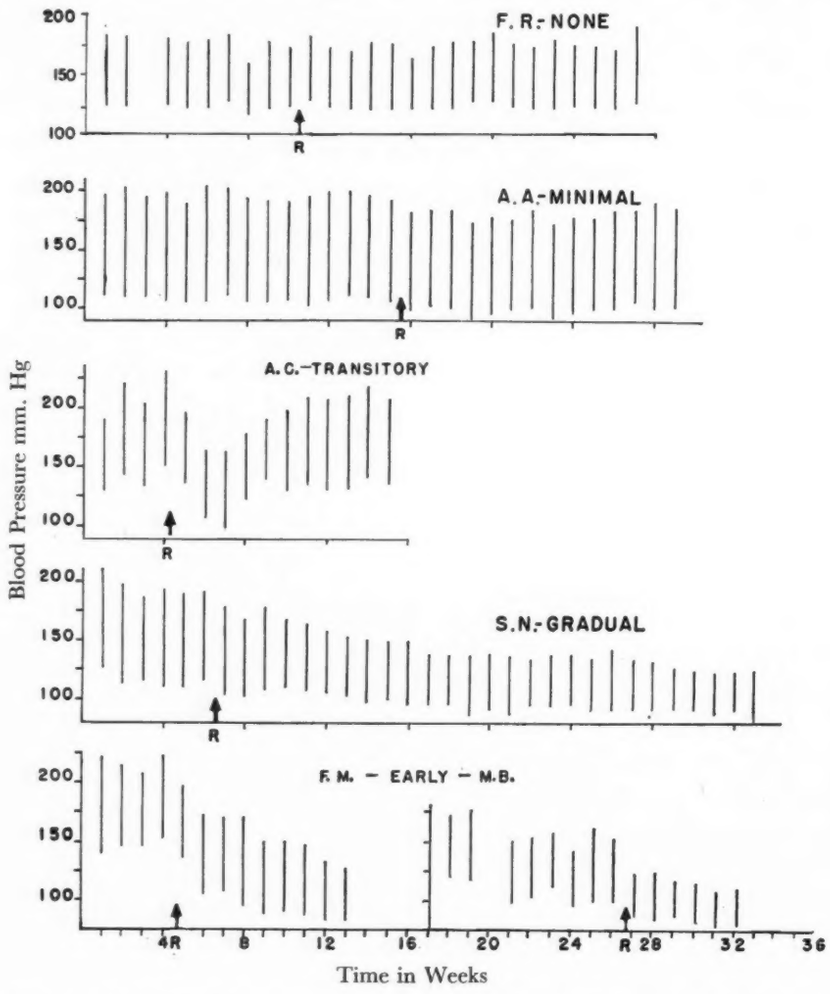

FIG. 3. The five most common types and rates of response of basal blood pressure to the rice diet. The top of each bar indicates mean basal systolic pressure for one week; the bottom of each bar indicates mean basal diastolic pressure for that week. The arrow, R, indicates beginning of rice diet period.

The effects of *addition of salt and various foodstuffs* to the rice diet were studied also. Without informing the patients, six subjects, three males and three females, were given capsules containing 1.0 gm. sodium chloride three times

daily from the start and throughout the first month of the rice regimen. None of these patients showed any fall in blood pressure. On withdrawal of the salt supplement one (A. D., Fig. 4) responded with a prompt and marked fall in both systolic and diastolic pressure; return to higher levels. This type of experiment also is under further study.

Preliminary efforts have been made to determine how far the unmodified Kempner rice regimen may be diversified without serious sacrifice of the effects on blood pressure, at least

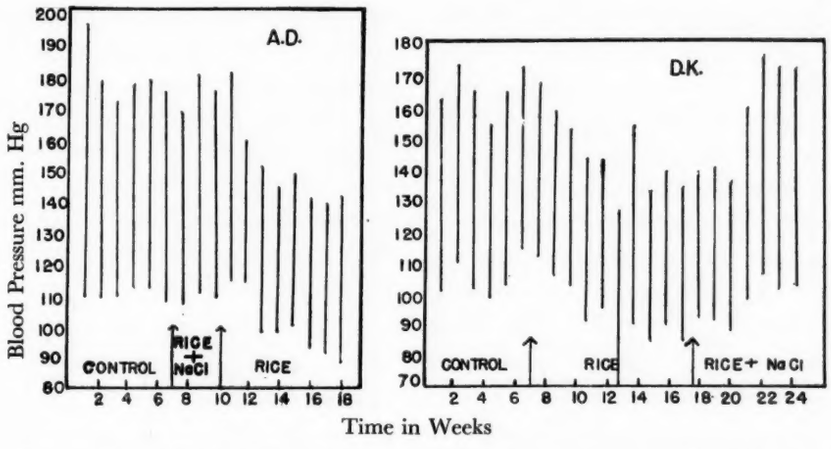

FIG. 4. Case A.D.: Failure of blood pressure to fall when, without knowledge of patient, 3.0 gm. NaCl daily was added in capsule form at the start of the rice diet; blood pressure fell rapidly when salt was withdrawn. Case D.K.: Addition of 1.0 gm. NaCl daily in capsule form to otherwise unmodified rice diet caused early return of blood pressure toward control levels after good response to rice diet had been obtained.

another (A. A.) showed a fall of 18 mm. Hg systolic and 12 mm. Hg diastolic; the remaining four patients (Cases F. Ru., M. Su., C. V. and An. Wa.) failed to show any subsequent response in blood pressure to the rice diet. This failure to respond subsequently to the rice diet presumably was due to an unhappy selection of patients. Further work along these lines is in progress to clarify the matter.

A second series of experiments was performed in which the sugar of our placebo capsules was replaced with sodium chloride in six patients after the blood pressure had responded well to the rice diet. In three patients (Cases F. Sm., M. Be. and J. Cl.) addition to the rice diet of 1.0 gm. sodium chloride three times daily for six, five and three weeks, respectively, resulted in rises usually within a week of +19/+8, +22/+11 and +38/+22 mm. Hg. In one patient (Case D. K.) addition to the rice diet of only 1.0 gm. sodium chloride daily for a period of five weeks resulted in a rise of +34/+14 mm. Hg. (Fig. 4.) On the other hand, in two patients (Cases P. K. and J. Co.) the daily addition of 3.0 gm. and 1.0 gm. sodium chloride for five and two weeks, respectively, caused no appreciable change in blood pressure; resumption of the control diet, however, caused a speedy in some cases. Addition to the rice diet of sodium-free protein and butter fat in the form of lonalac® (usually about 50 gm. dry weight daily as milk beverage or added to ground rice cereal) was not associated with an unequivocal rise in blood pressure in twenty-two patients tested. We have also tried the effects of adding to the rice diet low-sodium vegetables (two servings daily of 100 gm. tomatoes, cabbage, broccoli, mushrooms, onions or eggplant); corn and peanut oils (20–40 gm. daily in the form of fried rice or fried rice meal mush); low-sodium macaroni or spaghetti (100 gm. daily in place of one serving of rice); low-sodium matzoths ad lib; Borden's Instant coffee (1 to 3 cups daily). Given singly or in various combinations of two or three, these foods usually did not cause significant elevations of blood pressure above those achieved with the unmodified rice diet. Addition of thoroughly boiled beef or chicken (100 gm. per meal) also seemed satisfactory in two trials. More work along these lines is in progress.

Our observations therefore are in accord with the general experience that the effectiveness of the rice diet in regard to lowering of blood pressure is related largely

to its very low sodium chloride content. We have been unable to make out any significant positive or negative correlation between changes in systolic or diastolic pressure and age or sex of the patient, systolic or diastolic pressures at the end of the control period, changes in weight on the rice diet or alterations in serum sodium or other electrolytes.

Of considerable interest in connection with the response of blood pressure to the rice diet are the effects on *cardiac output*, as determined by cardiac catheterization, and on calculated *peripheral vascular resistance*.

For these data we are greatly indebted to Doctors Richard T. Cathcart, William W. Field and Dickinson W. Richards of the First (Columbia University) Medical Service, Bellevue Hospital. In Case B. P. the blood pressure by arm cuff in the control period immediately preceding cardiac catheterization was 240/165 mm. Hg, mean femoral arterial pressure 192–198 mm. Hg, mean cardiac output 6.5 L./minute, calculated peripheral resistance 2390 dynes cm.$^{-5}$ second; after eighteen weeks on the rice diet with good response the blood pressure by arm cuff was 190/110 mm. Hg, mean femoral arterial pressure 152–156 mm. Hg, mean cardiac output 6.4 L./minute (an inappreciable decline), calculated peripheral resistance 1935 dynes cm.$^{-5}$ second (a significant fall). In Case C. R. the blood pressure by arm cuff in the control period was 220/125 mm. Hg, mean femoral arterial pressure 154–158 mm. Hg, mean cardiac output 4.6 L./minute, calculated peripheral resistance 2705 dynes cm.$^{-5}$ second; after fourteen weeks on the rice diet with fair response the blood pressure by arm cuff was 190/110 mm. Hg, mean femoral arterial pressure 124–130 mm. Hg, mean cardiac output 4.4 L./minute, calculated peripheral resistance 2305 dynes cm.$^{-5}$ second (a significant fall). In Case W. H. the blood pressure by arm cuff in the control period was 220/124 mm. Hg, mean femoral arterial pressure 168–172 mm. Hg, mean cardiac output 4.6 L./minute, calculated peripheral resistance 2980 dynes cm.$^{-5}$ second; after nine weeks on the rice diet with no response the blood pressure by arm cuff was 208/120 mm. Hg, mean femoral arterial pressure 164 mm. Hg, cardiac output 4.7 L./minute, calculated peripheral resistance 2770 (insignificant fall).

These data indicate that a favorable response to the rice diet in respect to arterial blood pressure levels is not associated with a significant decline in cardiac output but is a reflection of significantly lowered peripheral vascular resistance.

The relation of the response in blood pressure to the *amytal floor* is of interest since Kempner[3] has reported that blood pressure levels on the rice diet may fall below the pretreatment amytal floor. The following tabulation lists the amytal floor and the lowest weekly basal pressure recorded in the control period, together with the lowest weekly basal pressure recorded in the rice diet period in the 19 patients studied:

Patient	(*a*) Lowest Basal Pressure, Control Period (mm. Hg)	(*b*) Amytal Floor, Control Period (mm. Hg)	(*c*) Lowest Basal Pressure, Rice Period (mm. Hg)	$\Delta\ b - c$ (mm. Hg)
C. A.	182/100	168/102	142/ 81	−26/−21
H. Col.	202/109	170/ 90	191/ 94	+21/+ 4
R. C.	182/106	150/ 92	172/101	+22/+ 9
H. F.	171/ 86	120/ 70	125/ 69	+ 5/− 1
C. H.	158/110	140/110	133/ 86	− 7/−24
S. La.	159/106	142/ 95	143/100	+ 1/+ 5
B. P.	170/107	158/110	131/ 93	−27/−17
G. R.	201/117	184/100	191/105	+ 7/+ 5
F. Ru.	172/123	148/108	174/121	+26/+13
M. Ba.	212/142	194/146	185/132	− 9/−14
M. Be.	144/ 96	108/ 94	108/ 79	0/−15
Ma. C.	195/ 88	168/ 85	154/ 66	−14/−19
J. Cl.	185/ 87	160/ 90	140/ 72	−20/−18
D. K.	151/ 99	156/104	131/ 85	−25/−19
M. Kn.	205/ 87	170/ 85	153/ 72	−17/−13
S. Lau.	224/119	206/120	200/108	− 6/−12
I. Mu.	215/109	162/ 98	172/ 94	+10/− 4
H. O.	235/133	210/122	188/100	−22/−22
H. S.	196/101	188/102	148/ 78	−40/−24
Means:	187/107	163/101	157/ 91	− 6/−10

It will be noted that the lowest basal systolic blood pressure readings in the control period invariably exceeded the systolic readings under amytal narcosis, usually by more than 20 mm. Hg. Diastolic readings showed smaller discrepancies but again were almost invariably higher. The lowest basal blood pressure readings obtained in the rice diet period, on the other hand, in eleven patients showed systolic levels that were lower than those obtained under amytal

in the control period; basal diastolic readings in fourteen patients were below the amytal floor; and in eleven cases both basal systolic and diastolic readings fell below the amytal floor.

Cold pressor tests were made by the standard technic in thirty-three patients, while at rest in bed, during the control period and again after six to eight weeks on the rice diet. Hyperreactor responses characteristic of essential hypertension were obtained in all but two instances, most increases in pressure in the "cold minute" falling in the range 30–60 mm. Hg systolic and 25–50 mm. Hg diastolic. There was no marked or consistent change in cold pressor response of these patients on the rice diet. Comparison of the distribution of points plotted for one period against the other revealed wide scatter with equal distribution of changes both in systolic and diastolic pressure above and below the 45° "no change" diagonal.

Hypertensive Retinopathy. Adequate descriptions by consultant ophthalmologists in both control and rice diet periods, and in some instances also eyeground photographs, are available for analysis in thirty-six patients presenting initial hypertensive retinopathy of grade II or more by the Keith-Wagener-Barker classification. To insure uniformity, repeated funduscopic examinations were made throughout the control and rice diet periods by the same consultant, Dr. Howard E. Wiener. According to the Keith-Wagener-Barker system of classification, grades I and II refer to vessel caliber and related changes only; grade III includes superimposed exudates, hemorrhages, retinal edema or peripapillitis; grade IV is characterized by the presence of papilledema. The mean duration of the control period in this group of patients was nine weeks, that of the rice diet period thirteen weeks. The incidence and nature of spontaneous changes in hypertensive

TABLE V

CHANGES IN RETINOPATHY OBSERVED DURING CONTROL PERIOD (MEAN DURATION: 9 WEEKS) AND RICE DIET PERIOD (MEAN DURATION: 13 WEEKS) IN THIRTY-SIX PATIENTS WITH ESSENTIAL HYPERTENSION

Classification of Retinopathy:				Improved				No Change				Worse			
Keith-Wagener-Barker Grade	Number of Patients			Control Period		Rice Period		Control Period		Rice Period		Control Period		Rice Period	
	Start Control Period	End Control Period	End Rice Period	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
II	14	12	17	2	14	7	58	8	57	5	42	4	29	0	..
III	15	17	15	5	33	14	82	9	60	3	18	1	7	0	..
IV	7	7	4	2	29	6	86	5	71	1	14	0	0	0	..

TABLE VI

CHANGES IN FUNDUSCOPIC SIGNS IN CONTROL PERIOD AND IN RICE DIET PERIOD IN THIRTY-SIX PATIENTS WITH ESSENTIAL HYPERTENSION

	% Improved		% No Change		% Worse	
	Control Period	Rice Period	Control Period	Rice Period	Control Period	Rice Period
A-V ratio	6	28	80	72	14	0
Arteriolar color	0	17	92	83	8	0
Local caliber changes	3	36	80	64	17	0
Arteriolar light reflex	0	6	100	94	0	0
A-V crossing signs	6	6	83	94	11	0
Exudates	14	63	72	37	14	0
Hemorrhages	14	63	59	37	27	0
Retinal edema	56	81	22	19	22	0
Papilledema	29	86	57	14	14	0

retinopathy to be anticipated with nonspecific therapy has already been indicated in our introductory paper.[10]

Control period (Tables v and vi): Of the fourteen patients showing initial grade ii retinopathy four exhibited progressive retinal vessel changes during the control period: increased vasospasticity, A-V crossing signs, pallor and sheathing. Two of these four patients advanced to grade iii classification because of the development of one retinal hemorrhage and exudate in one instance and an area of hemorrhage in the other. Two patients in this group showed improvement in A-V ratio, in the frequency and degree of crossing signs and in spastic phenomena but remained in grade ii.

There was no change in classification during the control period of the fifteen patients initially placed in grade iii. However, one patient developed increased peripapillary edema, hemorrhages, exudates and venous congestion under observation; five patients, while not regressing to grade ii, showed spontaneous reduction in peripapillary edema, some resorption of exudates and reduction in the number of hemorrhages.

Of the seven patients with papilledema (grade iv) two showed some improvement in the control period, one exhibiting reduction in peripapillary edema, the other spontaneous decrease in papilledema and lessened spasticity of retinal vessels. Neither case, however, could be reclassified in grade iii.

Rice diet (Tables v and vi): Improvement in retinopathy was much more marked in the rice diet period than in the control period and in not a single instance was there unequivocal worsening. Of the twelve patients classified in grade ii at the end of the control period, regression was noted in seven, the most frequent change being improvement in the A-V ratio and other vasospastic phenomena, lessening of pallor, crossing signs and tortuosity of vessels.

On the rice diet there was distinct remission of retinopathy in fourteen of the seventeen patients classified in grade iii at the end of the control period. Five showed complete clearing-up of retinal exudates and hemorrhages and were reclassified in grade ii. The nine remaining patients either had substantial reduction in the number and extent of retinal hemorrhages or exudates, or reduction or disappearance of peripapillitis. Associated vascular phenomena were of lesser degree in ten of the fourteen cases.

Resolution of papilledema, together with reduction but not complete dissolution of hemorrhages and exudates occurred in three of the seven patients in grade iv, these patients being reclassified in grade iii. Three additional cases showed measurable reduction but not disappearance of papilledema, accompanied by a decrease in hemorrhages and exudates. Two of these six patients also showed distinct improvement in associated retinal vessel changes. One patient with grade iv retinopathy proved wholly refractory to the rice diet.

There was no significant difference in response of basal systolic or diastolic blood pressure between those patients who showed distinct improvement in retinopathy and those who failed to do so.

These data are, of course, much more limited and less impressive than Kempner's extensive and well documented experience with amelioration of hypertensive retinopathy by the rice diet.[3,4] They are of the same general tenor, however. There can be no question that the incidence and degree of regression of hypertensive retinopathy observed on the rice regimen exceeds the probabilities of spontaneous resolution. However, it should be noted that worsening of improved eyeground changes occurred in seven patients upon resumption of a regular diet while under observation in the hospital.

Electrocardiographic Changes. The characteristic electrocardiographic abnormalities found in many patients with essential hypertension tend either to show slow progression or to remain essentially unchanged for long periods and are widely held to be of unfavorable prognostic import. However, spontaneous changes toward normal, as indicated by a tendency of inverted

T waves to become upright and depressed S-T segments to become isoelectric, are occasionally observed particularly in women. In our introductory study of the effects of prolonged hospitalization *per se*[10] it was found that such changes toward normal occurred in six of forty-one patients.

F., T_1 and Tv_5 tended toward upright, T_2 became more distinctly upright. In Case M. Ba., T_1 and Tv_5 changed from inverted to upright, T_2 became more definitely upright.

Rice diet: Of the remaining twenty-seven patients who showed no modification of the ECG during the control period, nine (all male save one) developed changes toward a more normal pattern in the rice diet period (Fig. 5); eighteen remained the same; none showed progression. However, one patient (Case F. B.) not included in the group of twenty-nine because the ECG on admission showed changes suggestive of old posterior wall infarction developed another myocardial infarction in the eighth week of the rice diet.

TABLE VII

ANALYSIS OF ASSOCIATED RELEVANT DATA IN NINE PATIENTS WITH AND EIGHTEEN PATIENTS WITHOUT ELECTROCARDIOGRAPH CHANGES TOWARD NORMAL ON THE RICE DIET

	No. of Patients	Duration of Control Period (wk.)	Time on Rice Diet (wk.)	Change in Basal Diastolic Pressure (mm. Hg)		Change in Heart Size (cm.)		Change in Body Weight (kg.)	
				Control	Rice	Control	Rice	Control	Rice
Changes toward normal in ECG	9	....	....	.....	.....	.....	.....	.....	.....
C. A., ♂ 58	..	11	15	− 4	−13	−0.3	−0.8	+0.7	−3.2
Mu. C., ♂ 57	..	12	4	− 4	− 3	.....	.....	−4.9	−1.9
F. H., ♂ 49	..	6	13	− 4	−19	+0.1	−0.9	−0.5	−5.8
M. Kn., ♀ 57	..	12	9	− 7	−20	+0.7	−0.3	−0.6	−5.1
S. N., ♂ 52	..	6	28	−10	−30	+0.5	−1.7	−3.3	+3.0
C. Ro., ♂ 49	..	11	28	+ 8	− 7	+0.4	−0.2	+0.9	−1.1
F. Sm., ♂ 64	..	15	29	− 1	−17	.....	.....	+0.9	+4.5
F. M., ♂ 40	..	3	17	+ 7	−63	0.0	−3.5	−2.0	−7.9
J. L., ♂ 58	..	3	12	−16	0	.....	.....	−0.1	−5.5
No change in ECG on rice diet.	18	Means: 8.8 Means: 8.4	17.2 12.3	− 3.4 − 4.4	−19.0 −11.5	+0.2 0	−1.2 −0.7	−0.8 +0.4	−2.6 −0.8

Kempner[3] reported a much higher proportion of such reversions toward normal in his hypertensive patients on the rice diet. Of ninety-nine subjects with pretreatment inversion of T_1, in thirty T_1 became upright.

In the present study electrocardiographic tracings of the three standard limb leads and V_5 were recorded at the beginning and end of the control period and again every four to six weeks during the rice regimen. Twenty-nine patients were found to have abnormal electrocardiograms when admitted to this Service, exclusive of those receiving digitalis.

Control period: In two instances, Cases H. F. and M. Ba., electrocardiographic changes toward normal occurred during the control period (see Fig. 4, reference 10). In Case H.

As indicated in Table VII, the mean duration of the rice period was 17.2 weeks in the nine patients who showed changes toward normal as compared with 12.3 weeks in those who did not, and the control period was shorter in both instances (8.8 and 8.4 weeks, respectively). It will be noted in Table VII that there were no significant differences in respect to mean changes in

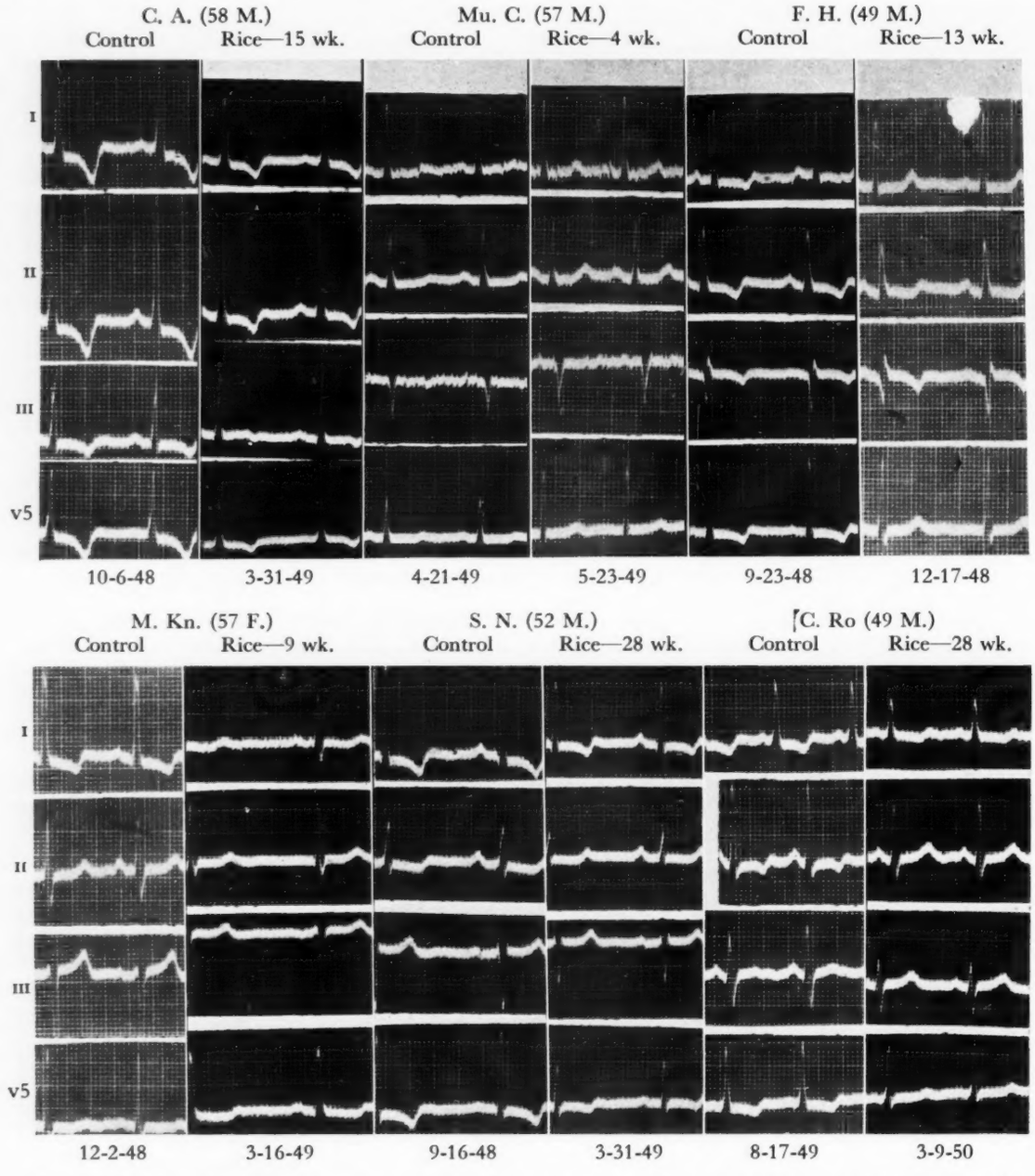

FIG. 5. Electrocardiograms in control period and rice diet. C. A.: Less marked inversion T_1, T_2, Tv_5 after fifteen weeks on rice diet. MU. C.: T_1, T_2, Tv_5 more upright after four weeks on rice diet. F. H.: T_1, T_2, Tv_5 changed from inverted to upright after thirteen weeks on rice diet. M. KN.: T_1 changed from inverted to upright after nine weeks on rice diet. S. N.: T_1 and Tv_5 became less inverted, T_2 became upright after twenty-eight weeks on rice diet. C. RO.: T_1, T_2, Tv_5 changed from inverted or diphasic to upright after twenty-eight weeks on rice diet.

diastolic pressure, heart size or body weight between those who did and those who did not show apparent improvement in the ECG. We considered the possibility that the high potassium content of the rice-fruit regimen might have something to do with reversion of T waves to upright but this was not reflected in higher serum potassium levels in the cases concerned; in general, hyperkaliemia does not develop on the rice diet.

The incidence of regression of electrocardiographic changes on the rice diet appears to be significantly higher than that

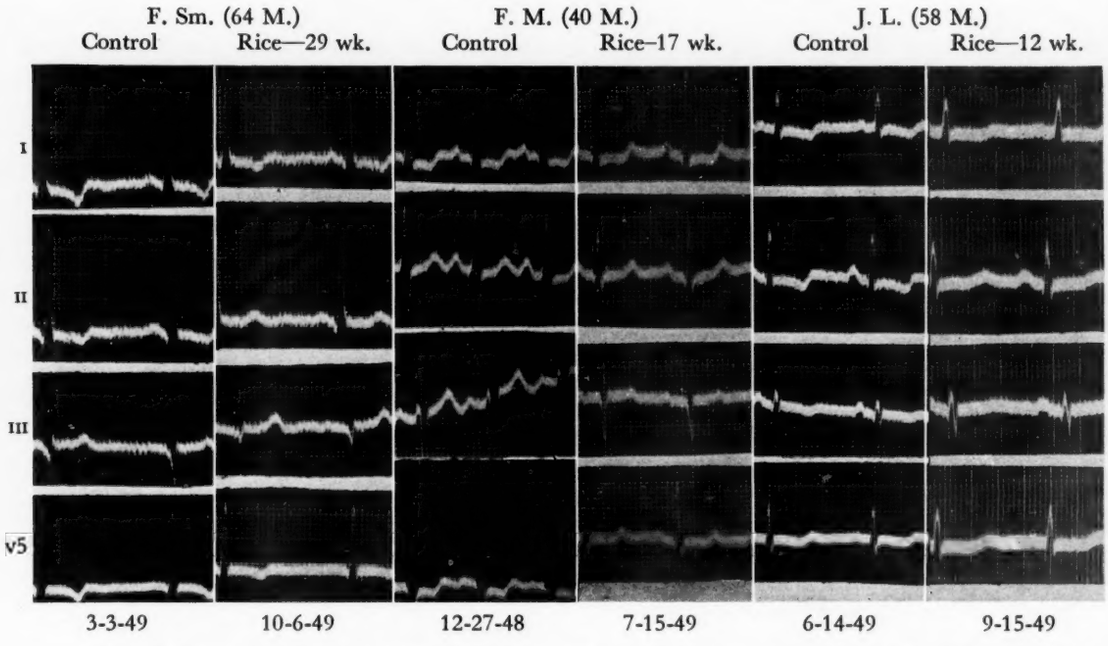

FIG. 5 (cont.). Electrocardiograms in control period and rice diet. F. SM.: After twenty-nine weeks on rice diet T_1 became less inverted and the depressed S-T segment in lead I became isoelectric, T_2 became upright, Tv_5 less inverted. F. M.: After seventeen weeks on rice diet the depressed S-T segments in leads I, II, V_5 became isoelectric or less depressed, T_1 and Tv_5 became more upright. J. L.: T_1, T_2, Tv_5 became upright or less inverted after twelve weeks on the rice diet.

to be expected spontaneously and occurred preponderantly in males in this series. However, in view of the multiplicity of factors involved both in causation and regression of electrocardiographic abnormalities in essential hypertension, and the lack of correlation with other indications of improvement, it is difficult to appraise the significance of the effects of the rice diet on the ECG. While presumably a favorable response, it is doubtful that the changes observed merit the emphasis placed upon them by Kempner who regards such alterations in the ECG as one of three major criteria in the estimation of improvement on the rice diet.

Heart Size. Enlargement of the heart is a common complication of essential hypertension and, as a prelude to or accompaniment of overt congestive failure, it is generally regarded as of unfavorable prognostic import. Kempner[3] found that the rice diet often effected a reduction in the transverse diameter of the cardiac silhouette. He reported a decrease of 10 per cent or more of the pretreatment measurement in 44 per cent of 286 patients who had been on the rice diet for a mean of 118 days and were not conjointly receiving digitalis. Increase in heart size occurred in only 5 per cent of these cases. The mean cardiac transverse diameter before treatment was 14.2 cm.; after rice diet therapy 12.9 cm.

In the present study satisfactory data on changes in heart size during the control and rice diet are available in thirty-three patients. Of these eighteen were receiving digitalis for varying degrees of cardiac decompensation and eight were in frank congestive failure at the time of admission.

Control period: At the beginning of the control period seventeen patients were found to have an increase in transverse diameter of the cardiac silhouette at least 20 per cent above prediction based on patient height and weight. At the end of the control period, which was of 9.7 weeks mean duration, the number had grown to twenty-one (Fig. 6). In only two cases was there a reduction in heart size greater than 1.0 cm. (Table VIII.) These two patients had partially regained compensation in the

control period, without significant fall in diastolic blood pressure or marked weight loss.

Rice diet: On the rice diet nineteen of the thirty-three patients were found to have had a reduction in transverse diameter of the cardiac silhouette greater than 1.0 cm., the mean decrease being 2.0 cm. (Table VIII.) There was a distinct shift downward in frequency distribution with respect to cardiac enlargement, nineteen of the patients falling in the groups less than 20 per cent above the predicted normal, as compared with twelve at the end of the control period. (Fig. 6.) The incidence of reduction in transverse diameter on the rice diet was thus considerably greater than occurred in the control period or in the previously reported study[10] of spontaneous variation and effects of hospitalization *per se* on heart size. It should be noted (Table VIII) that there was an insignificant difference in respect to duration of the rice diet period, fall in blood pressure and change in weight between those who did and those who did not show reduction in transverse diameter greater than 1.0 cm. Weight loss was too small to implicate reduction due to starvation.[30]

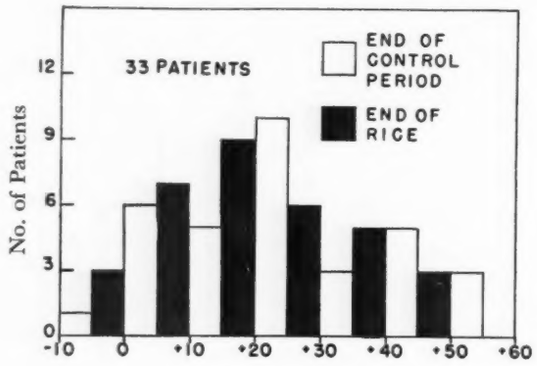

FIG. 6. Histogram representing frequency distribution of per cent deviation of measured from predicted (normal) transverse cardiac diameter in thirty-three patients with essential hypertension at the end of the control period (mean duration 9.7 weeks) and at the end of the rice diet period (mean duration 11.4 weeks). At the end of the control period twelve patients had heart sizes less than 20 per cent above prediction; in the rice diet period this number increased to nineteen. (For contrast with effects of hospitalization *per se*, see Fig. 3, reference 10.)

In considering the significance of this effect of the rice diet it should be recalled that increase in heart size in arterial hypertension is the result of cardiac *hypertrophy*, the effect of work against increased peripheral vascular resistance, and cardiac *dilatation*, a sign of the failing hypertrophied left ventricle. As already indicated, peripheral vascular resistance may decrease on the rice diet. Consequently there may have been some diminution of cardiac hypertrophy, even in the comparatively short period of observation, in those evincing reduction in heart size since the mean fall in basal diastolic pressure in this group was 20.6 mm. Hg as compared with 9.6 mm. Hg in the other. (Table VIII.) However, expansion of cardiac contours visualized roentgenographically ordinarily largely reflects dilatation of the heart—cardiac hypertrophy results in concentric enlargement which encroaches upon the ventricular lumen and is difficult to detect by x-ray. The changes noted in measurement of heart size therefore doubtless refer for the most part to variations in cardiac dilatation as a reflection of varying degrees of clinically manifest or occult cardiac failure.

TABLE VIII
REDUCTION OF TRANSVERSE DIAMETER OF CARDIAC SILHOUETTE IN CONTROL PERIOD AND IN RICE DIET PERIOD IN THIRTY-THREE PATIENTS WITH ESSENTIAL HYPERTENSION

	Reduction in Transverse Diameter	
	<1 cm.	>1 cm.
Control Period		
Number of patients	31	2
Mean change heart size, cm	+0.1	−1.2
Mean duration control period, wk	9.6	11
Rice Diet Period		
Number of patients	14	19
Mean change heart size, cm	−0.2	−2.0
Mean change diastolic pressure, mm. Hg	−9.6	−20.6
Mean weight change, kg	−2.0	−2.2
Mean duration rice diet, wk	9.9	12.5

The effectiveness of the extremely low salt content of the rice diet in restoring

cardiac compensation is apparent in the prompt and sometimes marked diuresis following institution of the rice diet, the lowering of elevated circulation time and venous pressure, and relief of clinical signs and symptoms of overt congestive failure. Digitalis frequently may be withdrawn; ten of the thirty-three patients required digitalis at initiation of the rice diet and in six it could be discontinued. The association of restoration of compensation in the failing, dilated heart with reduction in transverse cardiac diameter, at least when observed relatively early in the rice diet period, was quite apparent in some of our patients and probably applies even to those cases without clinically obvious failure since cardiac dilatation may long antedate overt symptoms and signs of congestion. Evidence for this is provided in the following section describing correlations between changes in heart size and plasma volume noted on the unmodified rice diet and on the rice diet when supplemented with salt.

T-1824 Dye Space. As a measure of plasma volume the T-1824 dye technic is subject to appreciable error, particularly in congestive failure, due to loss of dye into the interstitial and lymphatic fluid spaces and impounding of the dye in various blood depots.[31] Nevertheless the method gives reasonably consistent results and the T-1824 dye space is generally employed as a useful approximation of the circulating blood plasma volume.

In twenty-one patients T-1824 dye space was estimated toward the end of the control period and again on the rice diet at times that coincided with measurements of transverse cardiac diameter. Most of the subjects studied had some stigma of heart failure, either in the history or physical findings, or as indicated by increased venous pressure, circulation time or transverse cardiac diameter. In this important respect our study differs from that of Murphy[32] who excluded from his series all patients with clinical manifestations of heart failure although his data on pretreatment transverse cardiac diameter imply that some had increased heart size.

Control period: In accordance with previous reports[33,34] the T-1824 dye space was found to increase in rough proportion to the degree of cardiac failure as judged by the usual clinical and laboratory criteria. (Table IX.) For group I with minimal failure the mean T-1824 dye space was 2,940 ml., only 8 per cent above the average normal predicted on the basis of surface area.[33] This figure, which is in good agreement with Murphy,[32] implies that the fluid space into which T-1824 dye is distributed is little if at all expanded in patients with essential hypertension who show few or no indications of congestive heart failure. For group II with moderate failure the mean T-1824 dye space was 3,430 ml., or 23 per cent above the predicted normal. In the three patients with severe congestive failure, group III, the mean T-1824 dye space was 4,030 ml., or 55 per cent above the predicted normal.

Rice diet: After three to twelve weeks (mean 6.6 weeks) on the rice diet the T-1824 dye space was found in general to have contracted. (Table IX.) The mean decrease was 9 per cent of the control figures, the most marked reduction occurring in the three patients with severe congestive failure (mean: −20.3 per cent of the control dye space). Our data do not clearly indicate the rate of contraction of T-1824 dye space on the rice diet but Murphy[32] found that the reduction occurred chiefly in the first three to six weeks after initiation of the diet and remained relatively constant thereafter. It should be noted that in our series of twenty-one patients the mean over-all weight loss was only 2.5 kg.

In contrast to the lack of correlation between changes in heart size and diastolic blood pressure on the rice diet, a highly significant correlation could be made out with concomitant changes in T-1824 dye space, this correlation applying not only for patients with clinically obvious cardiac failure but for the group as a whole. (Fig. 7.) Such a relationship was not apparent in

Murphy's experience,[32] one reason probably being his selection of cases without overt congestive failure, as already mentioned. It should be pointed out that our correlation refers largely to measurements made within the first two months on the rice diet whereas, in both Kempner's experience and our own, reduction in transverse cardiac diameter may also occur later, long after major fluid shifts should have become stabilized. This would indicate that recompensation alone does not account altogether for reduction in

TABLE IX

T-1824 DYE AND THIOCYANATE SPACES IN TWENTY-ONE PATIENTS WITH ESSENTIAL HYPERTENSION

Patient	Surface Area (sq.m.)		Time on Rice Diet (wk.)	Absolute T-1824 Space, (ml.)			Absolute Thiocyanate Space (L.)		
	Control Period	Rice Period		Control Period	Rice Period	Change %	Control Period	Rice Period	Change %
Group I: Minimal Failure									
A. A.	1.60	1.58	3	2470	2430	− 1.6	14.3	10.8	−24
P. K.	1.81	1.81	12	3410	2940	−13.8	16.8	14.0	−17
C. Ro.	1.67	1.67	5	3220	2750	−14.6			
F. Ru.	1.81	1.75	7	3310	3440	+ 3.9	15.3	14.3	− 6.5
M. Ba.	1.61	1.62	9	2580	2480	− 9.5	15.5	14.7	− 5.2
M. Be.	1.53	1.50	4	2790	2630	− 5.7	12.3	10.8	−12
J. Co.	1.40	1.50	4	2380	2160	− 9.2	10.6	9.0	−15
I. Mu.	1.73	1.68	5	3370	3260	− 3.3			
Mean:			6.1	2940	2760	− 6.7	14.1	12.3	−13
% Above Predicted*				+ 8	+ 6				
Group II: Moderate Failure									
C. A.	1.70	1.68	9	3320	3010	− 9.3	15.6	14.0	−10
H. Col.	1.83	1.83	5	3740	3700	− 1.1			
R. G.	1.63	1.55	11	3480	3020	−13.2	19.7	14.2	−28
G. K.	1.68	1.56	3	3520	3520	0	16.7	13.0	−22
J. L.	1.80	1.68	6	4050	3720	− 8.2	17.1	15.1	−12
F. Sm.	1.85	1.90	7	4050	3770	− 6.9	20.4	16.1	−21
J. Cl.	1.40	1.40	4	2800	2300	−17.9			
C. D.	1.25	1.20	6	2510	2140	−14.8	13.5	11.4	−16
M. Kn.	1.83	1.80	9	4120	4050	− 1.7			
J. N.	1.67	1.63	3	2690	2650	− 1.5	13.0	11.9	− 8.5
Mean:			6.3	3430	3190	− 7.5	16.6	13.7	−17
% Above Predicted*				+23	+17				
Group III: Severe Failure									
B. L.	1.70	1.67	7	3940	3320	−15.7			
G. R.	1.78	1.72	10	4400	3350	−23.9			
E. M.	1.57	1.53	9	3760	2960	−21.2			
Mean:			8.7	4030	3210	−20.3			
% Above Predicted*				+55	+24				
All Cases Mean:			6.6	3330	3030	− 9.0	15.4	13.0	−15
All cases % Above Predicted:*				+22	+14				

* Predicted from Gibson and Evans[33] on basis of patient height and weight.

heart size on the rice diet, particularly after prolonged periods.

No definite correlation was found by Murphy or ourselves between changes in T-1824 dye space and fall in systolic or diastolic blood pressure although there was some indication in our data of a possible relation to marked falls in diastolic levels in patients with severe congestive failure.

That the contraction of T-1824 dye space observed on the rice diet was due to sodium restriction is demonstrated by the reexpansion occurring upon addition of sodium chloride to the rice diet in the five experiments summarized in Figure 8. As indicated, addition of 1.0 gm. and 3.0 gm. sodium chloride daily for periods of one to four weeks resulted in increased T-1824 dye space, the largest changes (up to 16 per cent above the rice period level) occurring with the larger salt supplement. Accompanying the expansion of plasma volume, although not closely paralleling it, was an increase in transverse cardiac diameter which was somewhat less than 1.0 cm. in three instances but exceeded 2 cm. in Case P. K. Systolic and diastolic blood pressures rose to levels intermediate between those of the rice diet and control periods in three of the patients but again there was no simple correlation with changes in T-1824 dye space. (Fig. 8.)

Thiocyanate Space. It has been made quite clear that, owing to entrance of thiocyanate into erythrocytes, gastric mucosa and probably other cells, the space into which thiocyanate ion is distributed is considerably larger than the extracellular fluid volume as measured, for example, by the inulin space.[35] The continuous infusion technic required for inulin space determinations seemed impracticable, however, in our patients with manifest or probable heart failure so measurements of changes in thiocyanate space on the rice diet were made in the hope that these might reflect shifts in plasma and interstitial fluid volumes.

Our findings in thirteen patients are in substantial agreement with those of Murphy[32] in seventeen cases of essential hypertension. In our series (Table IX) the mean thiocyanate space in the control period was 15.4 L., with reduction after a mean of 6.5 weeks on the rice diet to a mean of 13.0 L., or 85 per cent of the control value. The calculated "interstitial fluid space" in our series (thiocyanate space minus simultaneously determined T-1824 dye space) was reduced from a mean of 12.3 L. in the control period to 10.1 L. in the rice diet period, a reduction of 17.9 per cent. While there was a concurrent mean contraction in thiocyanate and T-1824 dye spaces, no generally applicable correlation between these quantities could be made out.

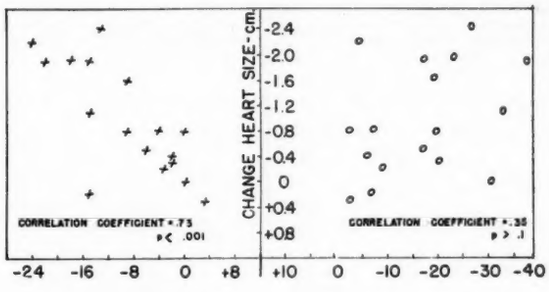

FIG. 7. Scatter diagram showing relation between changes in transverse cardiac diameter in roentgenogram and changes in plasma volume (T-1824 space) on left, and diastolic pressure on right, in seventeen patients with essential hypertension on the rice diet. There is highly significant correlation between changes in heart size and plasma volume, little correlation between changes in heart size and diastolic blood pressure.

Addition of 1.0 gm. sodium chloride to the rice diet in one case and 3.0 gm. in four others resulted in increased thiocyanate spaces in four of the five instances, the increase in two of the patients receiving 3.0 gm. salt being statistically significant. Apart from occurrence of the largest expansion of both thiocyanate and T-1824 dye spaces in the same patient (P. K.), again no simple relation between these changes could be established.

There can be no doubt that a contraction of extracellular fluid volume occurs on the rice diet, usually in the early weeks, and

that this reflects an initial loss of body sodium incidental to the extremely low sodium intake. From the changes in serum sodium concentration and in thiocyanate space in these thirteen patients over a mean period of 6.6 weeks on the rice diet we have made a first approximation of the extent of loss of total body sodium. In every instance sodium loss occurred, ranging from 54 to 847 mEq., the mean being 338 mEq. No significant correlation could be made out between the estimated decrease in body sodium and the decline in basal diastolic blood pressure.

The decrease in total body sodium in the initial weeks on the rice diet is not reflected in changes in concentration of sodium in the serum, which usually is maintained within

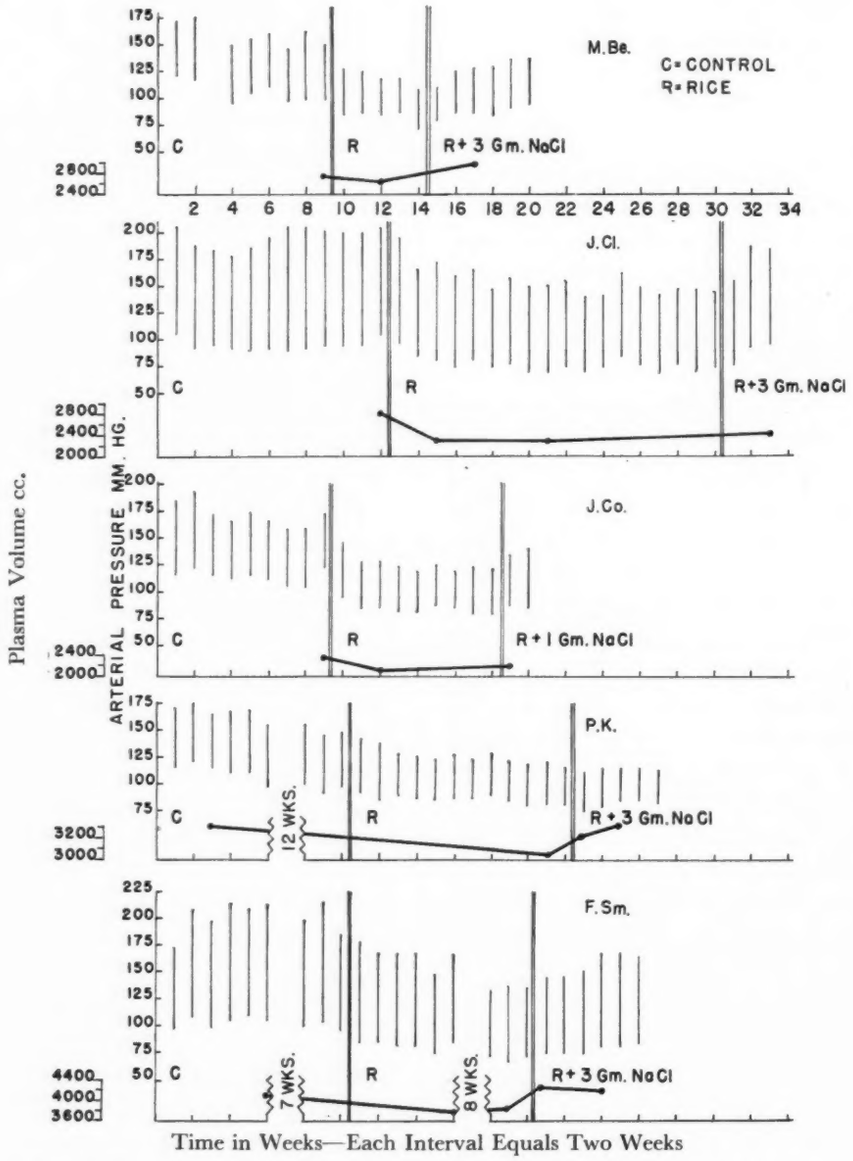

FIG. 8. Changes in arterial pressure and plasma volume (T-1824 space) in five patients with essential hypertension on strict rice diet and following addition of 1 or 3 gm. of sodium chloride daily. The top of each vertical bar indicates mean basal systolic pressure for one week and bottom of bar the corresponding diastolic pressure. The heavy line below indicates concomitant plasma volume changes.

normal limits. Similarly, as Murphy[32] has pointed out, the apparent stability of serum plasma protein concentrations on the rice diet is misleading because, in view of the contraction of plasma volume, there may be a substantial reduction in total circulating plasma proteins.

TABLE X

CHANGES IN BODY WEIGHT IN FIFTY PATIENTS WITH ESSENTIAL HYPERTENSION DURING THE CONTROL AND RICE DIET PERIODS

	No. of Patients	Control Period				Rice Diet Period			
		Weight Change		Duration		Weight Change		Duration	
		Mean (kg.)	Range (kg.)	Mean (wk.)	Range (wk.)	Mean (kg.)	Range (kg.)	Mean (wk.)	Range (wk.)
Males	28	+0.7	−4.9 to +5.7	9.4	3–20	−3.0	−8.3 to +1.0	10.9	3–20
Females	22	+2.0	−9.1 to +5.1	10.2	5–28	−1.9	−9.0 to +5.0	12.2	6–36
Total	50	+1.3	−9.1 to +5.7	9.8	3–28	−2.5	−9.0 to +5.0	11.5	3–36

Changes in Body Weight. *Control period:* There was a mean weight gain of 1.3 kg. for the group as a whole in the control period. (Table x.) Individual variations ranged from a loss of 9.1 kg. to a gain of 5.7 kg., reflecting adjustments in the diet to reduce the weight of some obese patients and to increase the caloric intake of others who were much below the standard. Some patients with cardiac decompensation also gained weight associated with water retention on the supposedly "low-salt" hospital diet which, as indicated, proved on analysis to average 10 gm. sodium chloride daily.

Rice diet: On the rice diet the over-all change in weight was only −2.5 kg. (Table x.) Thirteen males and nine females showed a weight loss greater than 2.5 kg. (maximum 9 kg.), fourteen males and nine females lost less than 2.5 kg., one male and four females gained up to 5 kg. in weight. Almost all patients lost appreciable weight in the first two weeks on the rice diet, usually in association with marked diuresis, and the weight loss was apt to continue at diminishing rates to about the sixth week. After the sixth rice diet week the weight generally remained constant or increased toward or above control levels. Excessive weight loss or gain was controlled by individual adjustments in the calorie intake of the rice regimen.

Antipyrine Space. Of interest is a comparison of body weight loss or gain on the rice diet with changes in total body water content, as estimated by the antipyrine

TABLE XI

CHANGES IN BODY WEIGHT AND ANTIPYRINE SPACE ON THE RICE DIET IN SEVENTEEN PATIENTS WITH ESSENTIAL HYPERTENSION

Patients	Body Weight (kg.)			Antipyrine Space (L.)			Water Loss > Weight Loss $\Delta f - c$
	(a) Control Period	(b) Rice Period	(c) $\Delta a - b$	(d) Control Period	(e) Rice Period	(f) $\Delta d - e$	
Males							
R. C.	56.5	57.0	+0.5	32.9	31.8	− 1.1	− 1.6
F. Ru.	62.9	62.9	0.0	34.0	32.0	− 2.0	− 2.0
A. A.	57.3	55.5	−1.8	32.0	28.0	− 4.0	− 2.2
A. D.	52.1	49.4	−2.7	28.4	22.1	− 6.3	− 3.6
B. P.	67.2	64.5	−2.7	32.3	20.4	−11.9	− 9.2
Mu. C.	65.0	62.3	−2.7	30.3	33.1	+ 2.8	+ 5.5
C. Ro.	57.9	54.8	−3.1	32.6	35.5	+ 2.9	+ 6.0
H. Col.	62.0	58.8	−3.2	38.9	32.9	− 6.0	− 2.8
T. Mc.	61.8	57.3	−4.5	34.4	33.0	− 1.4	+ 3.1
Females							
M. Ba.	61.4	64.5	+3.1	36.4	28.3	− 8.1	−11.2
J. Co.	52.1	52.7	+0.6	30.5	25.9	− 4.6	− 5.2
C. V.	57.1	57.2	+0.1	23.0	26.6	+ 3.6	+ 3.5
Y. R.	51.4	50.0	−1.4	23.9	20.6	− 3.3	− 1.9
M. Be.	63.1	60.4	−2.7	26.6	22.8	− 3.8	− 1.1
A. Mo.	70.0	67.3	−2.7	35.6	35.3	− 0.3	+ 2.4
I. Mu.	67.9	64.1	−3.8	31.8	25.6	− 6.2	− 2.4
D. K.	61.4	53.2	−8.2	33.0	27.4	− 5.6	+ 2.6
Males Means:	60.3	57.9	−2.4	32.9	29.9	− 3.0	
Females Means:	60.6	58.7	−1.9	30.1	26.6	− 3.5	
Total Means:	60.4	58.3	−2.1	31.6	28.3	− 3.3	

space.* Data for such comparisons were obtained in seventeen patients in the control period and again three to fifteen weeks after institution of the rice diet. (Table XI.) None of these patients was in frank congestive failure. The mean control period values for

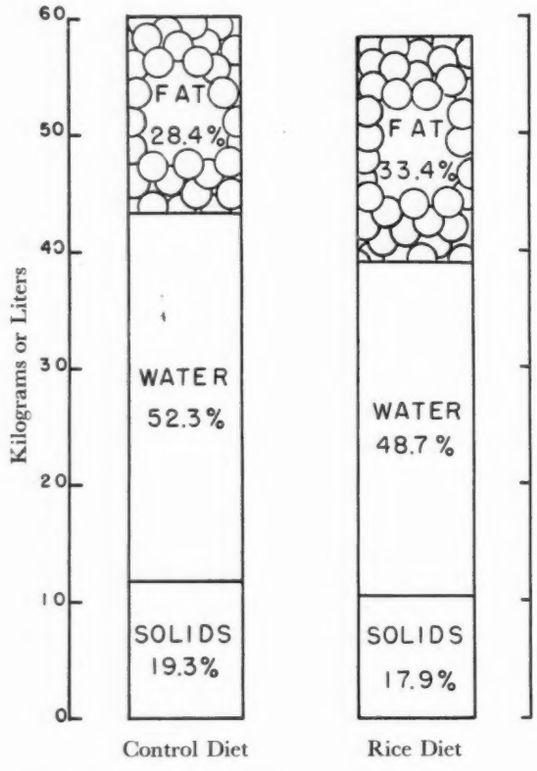

FIG. 9. Changes in body compartments on rice diet based upon averages of determinations of body weight and antipyrine space (total body water) in seventeen patients with essential hypertension. Solids compartment is calculated on the assumption that body water represents 73 per cent of lean body mass. On the rice diet there was slight weight loss with distinct increase in body fat at the expense of both water and solids compartments.

males (32.9 L.) and females (30.1 L.) are within the normal range.[25,36] A contraction of the antipyrine space occurred on the rice diet in all but three instances, including three patients (Cases R. C., M. Ba. and J. Co.) who gained weight. In eleven instances body water loss (mean: 3.3 L.) paradoxically appeared to be greater than body weight loss (mean: 2.1 kg.), presumably due to replacement of body water by fat. If the water content of the lean body mass can be assumed to remain constant at about 73 ± 3 per cent on the low sodium intake of the rice diet, the redistribution of fat, water and solids in our patients on the rice diet may be calculated to the following approximations (Fig. 9): The mean percentage of body fat increased from 28.4 to 33.4 per cent; body water decreased from 52.3 to 48.7 per cent; "lean body mass solids" decreased from 19.3 to 17.9 per cent.

Basal Metabolic Rate. A small but impressively consistent decline in basal metabolic rate was observed on the rice diet in our patients, of whom forty-three had tests performed at least twice during the control period and at least twice during the rice diet period. In our analysis of the results we have compared the lowest rate recorded during the control period with the lowest obtained during the rice diet period.

The mean of the lowest basal metabolic rates in the control period was +1.6 per cent, ranging from +32 per cent to −32 per cent; in the rice diet period the mean was −9.6 per cent, ranging from +17 to −33 per cent. The mean change in basal metabolic rate on the rice diet was −11 per cent, ranging from +17 to −39 per cent. Twelve males and nine females showed a drop greater than 10 per cent; eight males and seven females showed a drop which was less than 10 per cent; two males and two females showed a rise, in only one instance greater than 10 per cent; one male and two females remained unchanged.

Four factors probably contribute to this general decline in basal metabolic rate: training in technic and improved relaxation as the tests were repeated; improved cardiac compensation on the rice diet; increased ratio of fat to lean body mass; and perhaps also an apparent rise in respiratory quotient on the very high carbohydrate rice diet, even in the postabsorptive state. Determinations in three patients revealed respiratory quotients of 0.90, 0.92 and 0.86,

* We are greatly indebted to Doctors Marcelle F. Dunning and Eugene Y. Berger of the New York University Research Division, Goldwater Memorial Hospital, for the determinations of antipyrine space.

higher than the assumed respiratory quotient of 0.82.

Serum Electrolyte Levels and Related Observations. The extremely low sodium content of the Kempner rice regimen throws new light upon the extraordinary capacity of the organism to save base by adjusting its conservation mechanisms with hitherto unsuspected efficiency. As Kempner[3,4] has pointed out, the rice diet produces no significant change in mean serum sodium concentrations, the mean serum potassium level tends to rise slightly, serum chloride falls significantly and there is a significant increase in serum bicarbonate.

TABLE XII

INFLUENCE OF THE RICE DIET ON SERUM SODIUM, POTASSIUM, CHLORIDE AND BICARBONATE LEVELS

	Number of Patients	Control Diet (*a*)		Rice Diet (*b*)			
						Δ *a* − *b*	
		Mean mEq./L.	Range mEq./L.	Mean mEq./L.	Range mEq /L.	Mean mEq./L.	Range mEq./L.
Sodium	29	138.2	133 to 143	135.2	124 to 142	−3.0	−16 to +4.0
Potassium	13	4.3	3.7 to 5.3	4.6	3.3 to 5.9	+0.3	−0.7 to +1.5
Chloride	32	104.1	94 to 110	96.5	80 to 107	−7.6	−19 to −1.0
Bicarbonate	11	27.6	23.3 to 30.0	32.2	26.7 to 36.3	+4.6	+1.2 to +7.0

In our studies in twenty-nine patients with essential hypertension the mean serum *sodium* concentration fell insignificantly, from 138.2 to 135.2 mEq./L. (Table XII.) Six of these patients showed a rise in serum sodium on the rice diet, seventeen had decreases less than 5 mEq./L. and six showed greater decreases, in two instances the falls being 10 and 16 mEq./L. These falls were not accompanied by recognizable clinical manifestations of low-salt syndrome, unless general muscle weakness and the other diffuse complaints already described are to be so construed. Obviously, maintenance of normal serum sodium levels for many months in the face of negligible intake on the rice diet requires intact sodium conservation mechanisms in the kidneys,* gastrointestinal tract and skin. As Kempner[3] has shown, urinary excretion of sodium on the rice diet falls to extraordinarily low levels if the kidneys are not too badly damaged. Our experience is illustrated in Figure 10 which shows a typically precipitous drop in urinary sodium excretion upon institution of the rice diet, from 90 to 10 mEq. per day, followed by a gradual further decrease to levels of about 1 mEq. per day by the third week. Sodium balance studies to be reported elsewhere indicated essential sodium equilibrium after several weeks of the rice diet, the small negative or positive balances noted probably reflecting variations in collection of excreta.

In thirteen patients studied the mean serum *potassium* level rose on the rice diet from 4.3 to 4.6 mEq./L. (Table XII.) Five of these patients showed rises of more than 0.5 mEq./L., in no instance (except in one case of terminal glomerulonephritis not included in this series) reaching significant hyperkaliemic levels; in four patients there were increases less than 0.5 mEq./L.; and in four the serum potassium levels fell. Potassium excretion in the urine rose somewhat on the rice regimen. (Fig. 10.) Balance studies in eight cases indicated slight positive potassium balance after several weeks

* For this reason we have not, in conjunction with the rice diet, employed mercurial diuretics which are used by some to accelerate sodium depletion on low-salt diets. Use of mercurials would seem to be dangerous in counteracting the regulation of sodium excretion necessary to maintain physiologic serum sodium concentrations.

on the rice diet in some instances but with little deviation from apparent equilibrium.

The rice diet produced no significant change in serum *calcium* levels in any of the six patients studied. The daily urinary calcium excretion fell promptly to very low

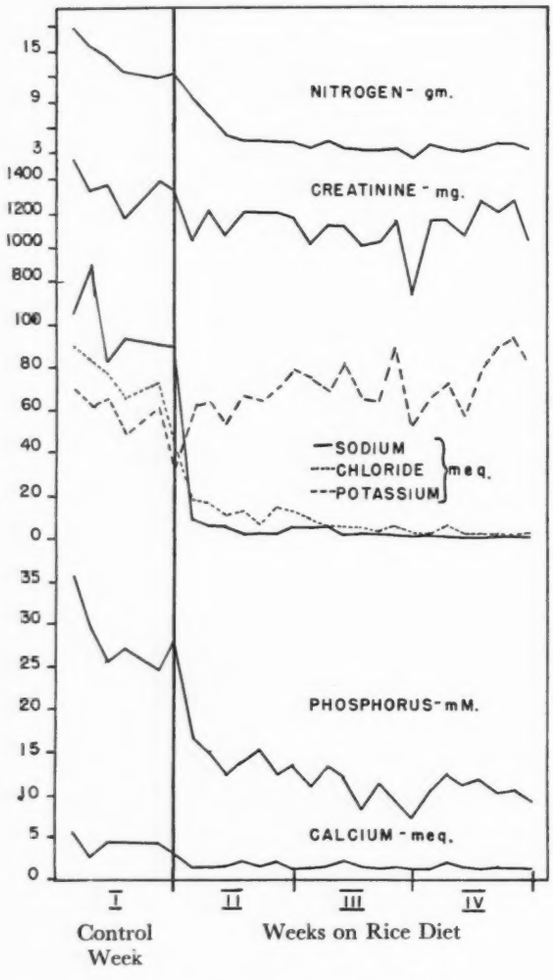

FIG. 10. Decreased urinary excretion of nitrogen, creatinine, sodium, chloride, potassium, phosphorus and calcium on the rice diet (Case W. H.). Patient was on a regular diet in the first week and began the rice diet at the point indicated by vertical line for start of the second week.

levels when the rice diet was instituted and remained at this level throughout the three weeks of urine collections. Balance studies in two patients revealed consistent and distinct negative calcium balance, reflecting the inadequate calcium intake on the rice regimen, with large losses of calcium in the stools.

The serum *chloride* level fell without exception in the thirty-two patients studied, from a mean pretreatment value of 104.1 mEq./L. to 96.5 mEq./L. on the rice diet. (Table XII.) In ten instances the decline was less than 5 mEq./L., in the remaining cases this figure was exceeded, reaching 17 and 19 mEq./L. in two patients. Excretion of chloride in the urine (Fig. 10) dropped precipitously upon institution of the rice diet, from levels of about 70 to 18 mEq. per day, thereafter declining gradually to daily levels of about 1.5 mEq. in the third week of the rice diet. Balance studies in five patients gave variable results impossible of interpretation.

The *bicarbonate* content of the serum rose in every one of the eleven patients included in this series, from a mean pretreatment level of 27.6 mEq./L. to a mean of 32.2 mEq./L. on the rice diet. (Table XII.) In five instances the increase was less than 5 mEq./L., in six the rise exceeded this figure. The regular development of compensated metabolic alkalosis on the rice diet is attributable, in part, to the fall in serum chloride and the high intake of readily oxidizable organic acids, in the form of potassium salts, particularly in the fruits and fruit juices of the diet.

Serum *inorganic phosphate* levels in the blood were not affected by the rice diet. As a reflection of the low phosphorus content of the diet the daily urinary phosphorus excretion fell promptly from about 25 to 15 mM per day and thereafter diminished gradually to levels of about 10 mM per day. Balance studies gave results varying somewhat above or below equilibrium in different patients, variations not clearly related to nitrogen balance and difficult to evaluate.

It has already been pointed out that, as emphasized by Murphy,[32] values for the concentration of various electrolytes in the serum may not reflect large and important decreases or increases in total body electrolyte stores. In the case of sodium, for example, a sizable decrease in total body

content appears to occur quite regularly on the rice diet, as indicated by contraction of the extracellular fluid volume, without appreciable change in serum sodium concentrations. In the case of chloride this loss presumably is even larger.

As already stated no correlation could be made out between the fall in blood pressure and loss of body sodium or the change in serum concentrations of sodium or other electrolytes.

Serum Cholesterol, Phospholipids, Cholesterol/Phospholipid Ratio and Neutral Fat; Liver Function Tests. As has been indicated, the unmodified rice diet is devoid of cholesterol and has a negligible fat content, being far more restrictive in these respects than any "low cholesterol" diet thus far extensively investigated. Since the intake of preformed cholesterol is eliminated and fat and protein sources of two- and three-carbon compounds for endogenous synthesis are reduced to the absolute minimum, the rice diet is an important research tool in investigation of fundamental aspects of endogenous lipid, in particular cholesterol, metabolism in man. From the clinical point of view, the rice regimen is of special interest as an extreme form of dietary management of arteriosclerosis, of course a major problem in hypertensive vascular disease, providing what would appear to be optimal conditions for restricting the amount of cholesterol available for deposition in the walls of the blood vessels.

In making such studies we were limited perforce to indirect measurements, changes in serum levels of cholesterol, phospholipids and neutral fats as a reflection of the rate of production and disposition of the lipids. That this indirect approach may nevertheless give significant information in relation to the incidence of arteriosclerosis in man is indicated by recent investigation. It has been established[37–41] that the mean serum cholesterol level of patients with overt coronary arteriosclerosis is significantly higher than that of apparently normal subjects of the same age period and that abnormally great fluctuations in serum cholesterol, often cyclical, are apt to occur. It would appear further that while the rise in serum cholesterol is accompanied by an increase in serum phospholipids, this latter increase often is not commensurate and when this occurs the cholesterol/phospholipid ratio therefore rises.[40,41] Although more data are needed to establish a correlation, such elevated cholesterol/phospholipid ratios may be a significant factor in the production of arteriosclerosis.[42,43]

Kempner[4] reported that in a series of hypertensive patients numbering over 500, sizable decreases in serum cholesterol were observed with the rice diet, larger than have been obtained by any other dietary means. In 363 patients whose pre-treatment levels exceeded 220 mg. per cent, which Kempner apparently considers to be the upper limit of normal, the average level decreased from 279 to 205 mg. per cent, an average decrease of 74 mg. per cent. In 148 patients whose initial concentration of serum total cholesterol was below 220 mg. per cent, the average level after the rice diet was 171 mg. per cent, as compared with the pretreatment mean of 186 mg. per cent, or an average decrease of 15 mg. per cent. Starke[44] in Kempner's clinic studied the serum cholesterol of 154 patients more intensively, with similar findings. The average total cholesterol level was 272 mg. per cent for all the cases. Decreases averaging 33 mg. per cent were noted in the group whose levels before treatment were below 220 mg. per cent. The hypercholesterolemic group showed an average decrease of 80 mg. per cent. In comparing these findings with our own it is important to note that the total cholesterol determinations were made by the Bloor method whereas our own data are based on the Schoenheimer-Sperry method, which gives lower values.

Control period: Table XIII presents our data on serum total cholesterol and cholesterol esters as per cent of total cholesterol in forty-one patients with essential hypertension for the last five-week period of pre-treatment hospitalization on a standardized regular diet. In eighteen patients the results of serum phospholipid determinations are also indicated.

TABLE XIII

SERUM CHOLESTEROL AND LIPID PHOSPHORUS DETERMINATIONS IN EIGHTEEN PATIENTS WITH ESSENTIAL HYPERTENSION*

Group A. Cholesterol:Lipid Phosphorus Ratio on Rice Diet below Predicted Value
Group B. Cholesterol:Lipid Phosphorus Ratio on Rice Diet as Predicted

Patient	Sex and Age	Last 5 Weeks of Control Period					Rice Diet—Weeks												Weight Change (kg.)
		1	2	3	4	5	1	2	3	4	5	6	7	8	9	10	11	12	
Group A:																			
C. Ro.	M 49	202		194	184	135	119	141		139		162		173		146		157	−1.7
		59%			69%	64%	74%	69%		65%		67%		72%		66%		68%	
					8.8	7.0	6.5	9.0		9.0		8.8		10.2		9.2		9.7	
A. A.	M 65	212	210	216	211	226	162	186	199		229		235		214				−2.3
		71%	70%	76%	73%	71%	66%	65%	65%		66%		61%		65%				
				9.1	8.9	10.1	9.0	12.0	12.0		12.3		15.3		12.5				
C. La.	M 54		372		376		263	250	262		265	218							−2.7
			74%		73%		67%	65%	68%		67%	65%							
			16.0		15.0		13.4	15.0	13.5		14.2	12.0							
Y. R.	F 44	282		292	278	303	221			242				247					
		69%		72%	72%	70%	67%			69%				68%					
		13.5		11.3	12.7	13.3				12.5				12.9					
A. Mo.	F 40	214		219		254		160		176		165		172		180			−3.0
		69%		72%		70%		66%		70%		69%		68%		69			
		9.3		9.9		11.0		9.2		10.1		8.8		9.3		9.4			
J. N.	F 45	234		251		213	223		212		222		211		239		186		−5.0
		71%		73%		71%	71%		70%		72%		68%		67%		68%		
		10.0		9.6		8.9	9.4		12.0		11.8		12.7		13.3		10.3		
M. Ki.	F 54	247	265		241		233	159		204		160		209					−1.6
		74%	73%		71%		73%	62%		74%		62%		60%					
		11.0	12.1		11.2		10.0	10.6		11.1		10.9		12.8					
M. Su.	F 66	204	217	204		238	230	233			254	279		218		231			+0.9
		72%	70%	71%		70%	69%	63%			61%	60%		59%		65%			
		9.8	9.9	9.7		10.8		12.5			12.1	16.3		14.1		12.1			
Group B:																			
R. G.	M 53	221	282	319	343	314		245	254		197	193			168		155		−6.5
		74%	68%	71%	72%	67%		74%	73%		71%	70%			71%		73%		
		9.6	11.8	12.5	13.6	15.0		11.5	11.6		9.7	9.6			9.8		8.6		
G. K.	M 48		254	259	257	204	180	213		204		177		200		192	171		−4.1
			71%	71%	69%	70%	71%	70%		75%		70%		72%		68%	70%		
			11.5	11.6	11.2	9.0	8.2	10.8		8.7		8.9		9.9		9.6	8.9		
R. C.	M 48	223		192		218	162		164				145	134					−0.2
		73%		71%		72%	68%		68%				68%	69%					
		11.0		10.1		10.1	8.7		8.5				8.7	8.2					
T. Mc.	M 46	290	312		247	257		241		213		201			164	168	194		−1.8
		72%	71%		68%	72%		69%		70%		70%			69%	70%	70%		
		12.2	13.9		12.0			10.4		9.8		10.2			9.4	8.6	9.2		
S. D.	M 52	194	218		190	196	175	179		147		158		183		168			−2.2
		72%	74%		73%	72%	73%			72%		69%		72%		73%			
		8.8	9.6		8.7	8.6	7.9	9.0		6.1		8.2		8.5		8.8			
S. La.	M 60	300		238		234	190	230											−1.4
		72%		70%		71%	72%	70%											
		11.0		10.6		10.1	8.9	9.7											
W. H.	M 59		256		236			216		176		196		189		189		188	−1.6
			72%		74%			76%		70%		65%		70%		68%		66%	
			10.2					8.9		8.0		9.1		9.5				10.8	
P. R.	M 60	175				205	192		144	154			118		122	133			
		73%				69%	68%		67%	71%			64%		66%	70%			
		8.5				9.6	9.2		7.6	8.1			6.9		7.2	7.0			
J. Co.	F 32		155		161		172	128		142		145		148					−1.6
			70%		72%		71%	73%		70%		73%							
			7.5		8.0		8.3	6.6		7.8		7.6		8.9					
D. K.	F 48	211		206		227		158		161		170		170		165			−2.7
		72%		71%		72%		69%		70%		74%		71%		73%			
		9.6		9.2		10.5		8.0		8.2		7.5		8.5		8.4			

* First row of figures indicates serum total cholesterol in mg. per cent; second row, per cent cholesterol ester of total cholesterol; third row, lipid phosphorus in mg. per cent.

TABLE XIII (*Continued*)*

SERUM CHOLESTEROL DETERMINATIONS IN TWENTY THREE ADDITIONAL PATIENTS WITH ESSENTIAL HYPERTENSION

Group C. Patients in Whom Only Cholesterol Data Were Obtained

Patient	Sex and Age	Last 5 Weeks of Control Period					Rice Diet—Weeks												Weight Change (kg.)
		1	2	3	4	5	1	2	3	4	5	6	7	8	9	10	11	12	
Group C:																			
B. P.	M 41		307	251	280	260	217	243		217		273	240						−2.8
			76%	70%	73%	75%	71%	69%		67%		64%	68%						
H. F.	M 53	240	218	192	213	212	179	162	209	188	192	193	193	191	210	205	190	194	−4.8
		71%	73%	71%	73%	71%	64%	70%	70%	67%	70%	69%	71%	70%	71%	73%	70%	69%	
F. H.	M 49	186	190			177	142	163	156	150	146	150	140	136	155	136	133	142	−5.8
		72%	72%			71%	67%	71%	69%	65%	66%	67%	66%	70%	68%	66%	64%	73%	
S. N.	M 52	181	164	205	202	185		150		149	135	131	112	138	121	117	113	122	−3.0
		70%	66%	77%	73%	68%		67%		67%	70%	66%	67%	72%	74%	63%	66%	71%	
G. R.	M 54	329	343	282	300	313	274	249	234	295	304	288	237	282	261	250	234	279	−5.1
		69%	68%	69%	69%	69%	69%	69%	69%	71%	68%	70%	65%	69%	67%	77%	65%	66%	
S. S.	M 45	204		234	216	207			177	178	170	181	164	156	179	167	154	133	−1.7
		75%		80%	74%	68%			68%	67%	64%	68%	65%	72%	73%	70%	71%	65%	
F. Sm.	M 64	173	151	184	185	186	117	144	154	151	156	144		169	158	133	162	155	+1.0
		74%	75%	76%	73%	74%	71%	65%	69%	74%	71%	70%		75%	73%	70%	73%	72%	
P. K.	M 59	202	213	205	220	224		212	207		178	173	194	168	165	167	162	160	−3.5
		73%	72%	71%	75%	74%		72%	69%		72%	70%	71%	68%	70%	71%	69%	72%	
C. A.	M 58	250	246	262	238	260	207	216	200	200	181	168	161	185	194			187	−3.9
		72%	72%	73%	72%	71%	71%	68%	69%	69%	67%	67%	64%	65%	69%			72%	
B. L.	M 60	163	193	174	184	199	139	150	134	130	159	161		172	157	157	167	155	−2.0
		71%	73%	72%	68%	70%	70%	69%	63%	62%	64%	69%		69%	69%	69%	64%	69%	
Al. Ma.	M 59		217	188	187	187		191	230		197	199	216	197	182	192	192	200	−4.6
			81%	71%	72%	69%		62%	66%		62%	64%	64%	61%	67%	68%	65%	65%	
S. Lau.	F 26	195	192	177	218	173	171	134	129	189	182		150		165			156	−4.2
		69%	72%	73%	73%	69%	74%	72%	61%	69%	65%		69%		69%			72%	
M. Ba.	F 40	230	185	176	204	216	186	180	217	214	226	192		199	204	198	211	222	+1.5
		70%	67%	73%	73%	72%	72%	67%	71%	67%	68%	69%		69%	70%	70%		66%	
D. B.	F 38		370	323		340		285	338	309	303		285						−0.4
			74%	77%		72%		67%	69%	64%	70%		59%						
C. D.	F 52	216	227	252	229	228	205	168	204	214	219	201	205	184	181				−2.6
		71%	71%	69%	72%	71%	65%	71%	65%	63%	67%	68%	64%	63%	62%				
J. Cl.	F 50	231	234	224		224	197	181	202	164	185	178		202	196	193	187	173	+1.3
		72%	73%	70%		73%	68%	71%	72%	70%	71%	71%		72%	70%	76%	71%	72%	
I. Mu.	F 48	210	225	230	224	223		169	168	175	162	172	161	174	169	167	162		−0.9
		70%	73%	73%	68%	71%		70%	70%	73%	67%	69%	70%	70%	70%	70%	68%		
H. O.	F 54	221	224		218	238	188	221	225	208	188	236	203	213		228	209	258	+3.9
		74%	70%		72%	74%	66%	69%	71%	68%	68%	69%	68%	69%		68%	66%	72%	
M. P.	F 46			200	236	189		194	175	162		153	187	152					−0.3
				75%	75%	70%		72%	67%	68%		68%	75%	69%					
H. S.	F 51	232		227	212	209	161	202	196	196	195	172	180		205	192			−2.9
		71%		71%	73%	74%	69%	70%	72%	70%	74%	69%	70%		74%	71%			
F. B.	F 55	245	239	237	256	250			239	250	249		193	214	205	220	167	178	−9.6
		69%	73%	68%	68%	69%			68%	64%	68%		66%	68%	67%	66%	69%	69%	
E. M.	F 70	225	213	211	224	212	172	168	175	192	178	197		178	175	180	202	181	−4.9
		72%	70%	68%	67%	71%	66%	71%	69%	68%	72%	69%		71%	70%	73%	69%	72%	
M. Be.	F 57	231	217	239			221	258	197	216	198								−2.3
		74%	73%	72%			68%	71%	69%	74%	73%								

* First row of figures indicates serum total cholesterol in mg. per cent; second row, per cent cholesterol ester of total cholesterol.

The frequency distribution of *serum total cholesterol* in these forty-one patients who subsequently were placed on the rice regimen is shown in Figure 11. It is apparent from inspection of the data that patients with essential hypertension, for the most part

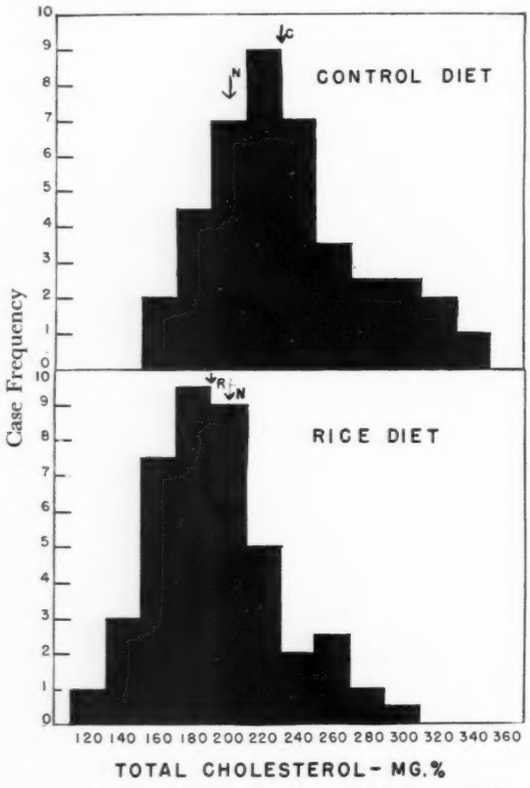

FIG. 11. "Smoothed" frequency histogram indicating distribution of mean total serum cholesterol levels in forty-one patients with essential hypertension on control and rice diets. Arrows N point to mean level of 201 mg. per cent observed in ninety-three normal individuals. Arrows C and R point to average levels in the hypertensive patients on control and rice diets, respectively.

without overt clinical or electrocardiographic evidences of coronary arteriosclerosis prior to or at the time of examination, frequently exhibit an elevated serum cholesterol level. The mean for the total cholesterol levels (Table XIV) was 231 mg. per cent, a figure which lies between the mean of 201 mg. per cent for a group of ninety-three normal subjects[45] and that of 262 mg. per cent for a group of sixty patients with a history of myocardial infarction.[45] Figure 11 indicates that thirty-one of these forty-one hypertensive patients (76 per cent) had serum total cholesterol levels above the normal mean.

Examination of Table XIII further reveals that many patients with essential hypertension also exhibit abnormally large fluctuations in serum cholesterol over a protracted

TABLE XIV
MEAN SERUM CHOLESTEROL CHANGES IN FORTY-ONE PATIENTS ON THE RICE DIET

	Mean Cholesterol Levels			
	Total mg. %	Free mg. %	Ester mg. %	Ester / Total %
Control diet	231 ± 39	65 ± 5	166	71.9
Rice diet	191 ± 36	60 ± 5	131	68.5
Change	−40	−5	−35	−3.4

period of observation; in nearly two-thirds of the cases the range between lowest and highest value exceeded 50 mg. per cent, as observed in persons with overt coronary arteriosclerosis.

The *cholesterol ester percentage of total cholesterol* in these forty-one patients was within normal limits (Table XIII), the mean being 71.9 per cent. (Table XIV.) This figure coincides with that obtained by Starke[44] in hypertensive patients, 72.0 per cent, and with the mean level of 72.7 per cent obtained by us in forty healthy, normotensive subjects. The fluctuations noted from week to week in our hypertensive patients on the control diet (Table XIII) must be ascribed in part to incorporation of the combined analytic errors of the determinations of free and total cholesterol.

The *relationship between serum total cholesterol and lipid phosphorus* during the control period was found to be linear. The equation for the regression line calculated from the data was $P = 2.08 + 0.035C$ in which lipid phosphorus (P) and total cholesterol (C) are expressed in mg. per cent. This is in close agreement with the findings in our series of healthy normotensive individuals, $P = 2.70 + 0.032C$, and corresponds with the equation found for normal and certain

abnormal subjects by Albrink, Man and Peters,[46] P = 3.3 + 0.032C.

Data on *serum neutral fats* were obtained in seventeen of our patients with essential hypertension in the fasting state. In the control period the levels in individual patients ranged from 300 to 670 mg. per cent, mean 420 mg. per cent, the fluctuations from time to time in any one patient often being of the order of 100 to 200 mg. per cent. It should be noted that analytic errors inherent in the method are large. Our values are considerably higher than those reported in healthy, normotensive subjects[47–49] which range from 100 to 300 mg. per cent as estimated by the different technics employed. Normal levels by our own technic are in the range 290 to 440 mg. per cent. Little relation was found between serum neutral fat and total cholesterol levels in our hypertensive patients.

Rice diet: Table XIII presents our data on serum total cholesterol and cholesterol esters as per cent of total cholesterol in these forty-one patients with essential hypertension while on the rice diet. In our analysis of these data the means of the values obtained during the second month on the rice diet were compared with the means for the last five weeks of the control period. (In Case S. La., however, data for the second month on the rice diet were lacking and those for the first month were used.) In eighteen patients the results of serum phospholipid determinations are also indicated (Table XIII, Groups A and B). In our analysis of the data on phospholipids and neutral fats all determinations in the control period and all during the rice diet period, except the first week, were employed to calculate means and make comparisons.

As indicated in Table XIV, there was a mean decline of 40 mg. per cent in *serum total cholesterol* content on the rice diet, from a pre-treatment mean of 231 ± 39 mg. per cent to 191 ± 36 mg. per cent. Figure 11 shows the frequency distribution of serum total cholesterol levels in these patients before and during the rice diet. The incidence of serum total cholesterol values within the normal range after the rice diet is clearly greater than before. While on the rice diet, thirty-five of forty-one patients, or 85 per cent, showed levels below the pre-treatment mean of the control period, and twenty-six patients or 63 per cent of the total showed levels below 201 mg. per cent, the mean for our group of healthy normotensive subjects.

Such comparisons of differences in means and in frequency distribution, however, give an incomplete and somewhat misleading picture of the response of the serum lipids to the rice diet. As reference to Tables XIII and XV will show, the individual response to the rice diet was extremely variable and quite unpredictable. In agreement with Starke,[44] in many cases a rapid and appreciable decline in serum total cholesterol was apparent in the first week, often leveling off before the end of the first month. In fact nearly all of the 40 mg. per cent mean decrease in serum total cholesterol observed in the second month on the rice diet actually occurred in the first or second week on the diet. Thus in the twenty-two patients in whom we have requisite data the mean serum total cholesterol level in the first week on the rice diet was 29 mg. per cent lower than in the last control period week. In thirty per cent of the patients the lowered level reached so rapidly was sustained throughout the period of observation on the rice diet (Fig. 12, 1A), but in about the same number the values rose somewhat again. (Fig. 12, 1B.) In about 25 per cent of the patients the decline in serum total cholesterol was gradual and slowly progressive as long as the patient continued on the diet. (Fig. 12, 2.) Fifteen per cent of the patients on the rice diet failed to show any statistically significant decrease in serum total cholesterol, or such wide cyclic fluctuations as were noted in the control period continued throughout the months on the rice diet (Fig. 12, 3), thus making interpretation of the effects of the diet difficult. In general it can be said that the proportion of cases showing abnormally great fluctuations, i.e., over a range greater than 50 mg. per cent, was somewhat de-

creased on the rice diet and the amplitude of the fluctuations tended to be smaller. (Fig. 12.)

The response of patients known to have had coronary occlusions or strokes was in no way distinctly different from that of the remaining hypertensive subjects with indeterminate degrees of arteriosclerosis. The magnitude of the decrease in serum total cholesterol did not correlate with the magnitude of changes in blood pressure on the rice diet, with changes in retinopathy, and only to a slight degree with weight loss (correlation coefficient = 0.3). The average weight loss over the period of observation, however, was only 2.4 kg. and, as indicated in Tables I and X, relatively few patients lost more weight than could be ascribed to water diuresis.

Further analysis of the data in Table XIII brought out the disturbing fact that most of the decline in serum total cholesterol noted was due to a sharp decrease in *cholesterol ester fraction* on the rice diet. Thus, as indicated in Table XIV, of the mean decrease in serum total cholesterol of 40 mg. per cent on the rice diet, only 5 mg. per cent was in the free cholesterol fraction and 35 mg. per cent was in the ester fraction, which fell from 71.9 to 68.5 per cent of the total cho-

TABLE XV

CHANGES IN SERUM LIPIDS AND LIVER FUNCTION ON RICE DIET

Group A. Cholesterol:Lipid Phosphorus Ratio on Rice Diet below Predicted Value

Group B. Cholesterol:Lipid Phosphorus Ratio on Rice Diet as Predicted

Patient	Sex	Serum Lipids												Liver Function Tests							
		Total Cholesterol (mg. %)		Lipid Phosphorus (mg. %)		Change % Ester Fraction on Rice Diet	mMols Cholesterol / mMols Lipid Phosphorus				Neutral Fat (mg. %)			BSP % Retention		Thymol Turbidity		Cephalin Flocculation 24 hr.–48 hr.		Dicumarol Tolerance	
							Found		Predicted												
		Control	Rice	Control	Rice		Control	Rice	Control	Rice	Control	Rice		Control	Rice	Control	Rice	Control	Rice	Control	Rice
Group A:																					
C. La.	M	320	250	13.3	13.7	− 7	1.9	1.5	2.0	1.8	670	780		4	12	3.7	4.4	0–0	0–0	.....	.....
C. Ro.	M	160	150	7.9	9.2	0	1.6	1.3	1.5	1.5	340	510		7	2	2.6	5.5	0–0	0–0	.....	.....
J. N.	F	240	210	9.7	12.0	− 4	2.0	1.4	1.8	1.7	450	780		15	17	5.8	14.5	0–0	2+ 2+	.....	.....
M. Su.	F	220	240	10.1	13.4	−10	1.8	1.4	1.7	1.8	370	920		2	..	4.8	18.2	0–0	0–1+	.....	.....
M. Ki.	F	250	180	11.6	11.4	− 8	1.7	1.3	1.8	1.6	460	640		2	17	4.0	8.7	0–0	0–0	20/45	53/120
Y. R.	F	290	250	12.7	12 7	− 1	1.8	1.6	1.9	1.8	520	450		13	21	5.6	4.5	0–0	0–0	.....	.....
A. A.	M	220	210	9.4	12.8	−10	1.9	1.3	1.7	1.7	430	900		7	11	1.7	10.5	0–0	0–0	.....	.....
A. Mo.	F	240	170	10.3	9.4	− 2	1.9	1.5	1.8	1.6	310	460		2	6	5.9	6.6	0–0	0–0	23/56	28/61
Means:		240	210	10.6	11.8	− 5.3	1.8	1.4	1.8	1.7	440	680									
													No. with Abnormal Tests:	2	5	0	5	0	1		
Group B:																					
T. Mc.	M	280	200	12.7	9.6	0	1.8	1.7	1.9	1.7	540	390		8	1	2.7	2.0	0–0	0–0	32/66	63/212
S. La.	M	280	210	11.2	9.3	0	2.0	1.8	1.9	1.7	300	330		25	15	2.4	1.6	0–0	0–0	.....	.....
R. C.	M	230	150	10.9	8.5	− 4	1.7	1.4	1.8	1.5	430	440		4	5	8.7	6.5	0–1+	0–1+	.....	.....
S. D.	M	190	170	8.6	8.1	− 1	1.8	1.7	1.7	1.6	320	400		2	3	4.2	3.8	0–0	0–0	.....	.....
W. H.	M	260	200	10.8	8.5	+ 1	1.9	1.9	1.9	1.7	...	...		7	13	6.9	8.4	0–0	0–0	22/52	26/96
D. K.	F	220	170	9.8	8.1	0	1.8	1.7	1.7	1.6	320	380		3	7	1.9	4.0	0–0	0–1+	.....	.....
P. R.	M	170	130	8.2	7.4	− 4	1.7	1.4	1.6	1.4	340	370		3	..	11.4	7.9	1+ 2+	1+ 2+	22/65	29/96
R. G.	M	290	190	12.5	9.8	+ 1	1.9	1.6	1.9	1.7	480	440		4	5	6.0	7.6	0–0	0–0	.....	.....
G. K.	M	240	190	10.8	9.5	0	1.8	1.6	1.8	1.7	560	490		2	4	1.1	2.0	0–0	0–0	.....	.....
J. Co.	F	160	140	7.8	7.3	+ 1	1.6	1.5	1.5	1.4	300	440		2	4	....	....	.....	.....	.....	.....
Means:		230	180	10.3	8.6	− 0.6	1.8	1.6	1.8	1.6	400	410									
													No. with Abnormal Tests:	1	2	4	4	1	1	.....	.....

lesterol (a mean fall of 3.4 per cent). A decline in cholesterol ester per cent of total cholesterol was the rule in our patients, the greatest change in this fraction observed being 10 per cent, but in a few cases the percentage remained the same. In general, the disproportionate decrease in cholesterol esters became apparent in the first week on the rice diet but usually became somewhat more pronounced as the diet was continued. It will be noted in Table XIII that considerable variation in the ratio occurred from week to week, part of which, as already pointed out, must be ascribed to incorporation of combined analytic errors.

Starke's data,[44] like our own, indicate clearly that, on the average, some 80 to 90 per cent of the fall in serum total cholesterol is due to a drop in cholesterol esters and that this ordinarily becomes evident in the first weeks on the rice diet. Unlike Starke's experience, however, no distinction in this regard could be made out in our relatively small group of patients between those who showed initial hypercholesterolemia and those who did not.

Analysis of the data in Tables XIII and XV in respect to changes in *serum phospholipids* on the rice diet in the eighteen patients studied brings out several additional points of interest. The phospholipid levels usually fell as the serum total cholesterol declined. However, in eight patients (group A, Tables XIII and XV) the altered serum lipid phosphorus level was higher than predicted from the equation of Albrink, Man and Peters, $P = 3.3 + 0.032C$, whereas in the remaining ten patients (Group B, Tables XIII and XV) the change in serum lipid phosphorus associated with the change in serum total cholesterol closely followed the regression equation. The two groups are contrasted in Table XV and Figure 13. Like the drop in serum total cholesterol and cholesterol ester, the differentiation in cholesterol/phospholipid ratio between these two groups of patients became apparent rapidly, generally within the first week on the rice diet although in two instances not until the patients had been on the diet for more than two months.

A similar division of our patients on the rice diet was observed in connection with changes in the *neutral fat* content of the serum. Seven of the patients in group A

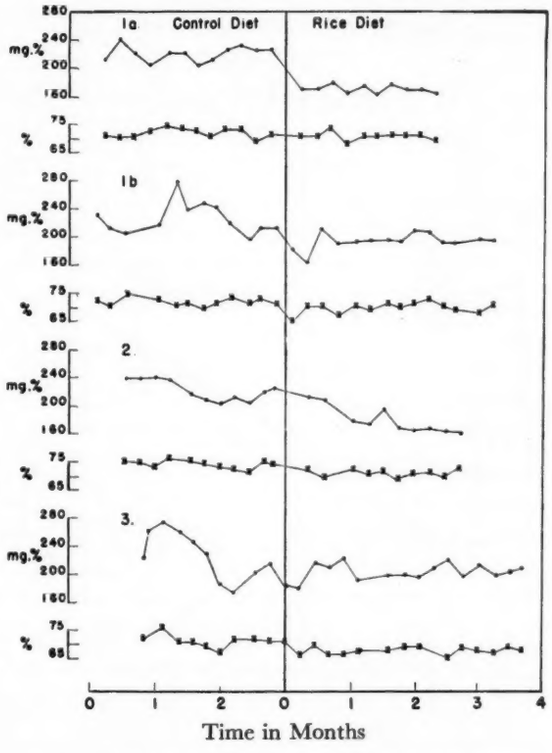

FIG. 12. Types of response of serum total cholesterol and cholesterol esters to institution of rice diet in representative patients. Dots indicate serum total cholesterol in mg. per cent; crosses indicate cholesterol esters as per cent of total cholesterol. Type 1*a*. Case I. MU. Rapid sustained drop in serum total cholesterol after institution of rice diet (30 per cent of cases). Type 1*b*. Case H. F. Transient drop in serum total cholesterol with partial or complete restoration of control level (30 per cent of cases). Type 2. Case P. K. Progressive slow decline in serum total cholesterol (25 per cent of cases). Type 3. Case M. BA. No significant change on rice diet (15 per cent of cases). The percentage of cholesterol esters tends to decrease slightly.

(Table XV) showed sizable increases in neutral fats whereas there was little change in the remaining cases. (Fig. 14.)

The collective data assembled in Table XV reveal that these several disturbances in serum lipids, i.e., the selective decline in serum cholesterol esters, the decreased cholesterol/phospholipid ratio and the increase in serum neutral fats, all tended to be

of parallel degree in any one patient on the rice diet, suggesting a common causal mechanism. The appearance of these phenomena could not be correlated with any prior observations made on the serum lipids in the control period or with changes in blood pressure, serum electrolytes, serum proteins or basal metabolic rate on the rice diet. The most obvious implication is that impairment of some phases of liver function may occur on the rice diet. This interpretation appears to be supported by the results of the BSP, thymol turbidity, cephalin flocculation and dicumarol tolerance tests included in Table xv. It will be noted that the percentage of positive tests, particularly the thymol turbidity test, rose on the rice diet in the patients constituting group A. Of interest in this connection is the report by Meyers and Murphy[50] that there is a decided decrease in BSP clearance by the liver in hypertensive patients on the rice diet, this decline appearing in the first few weeks on the diet and persisting for as long as three months.

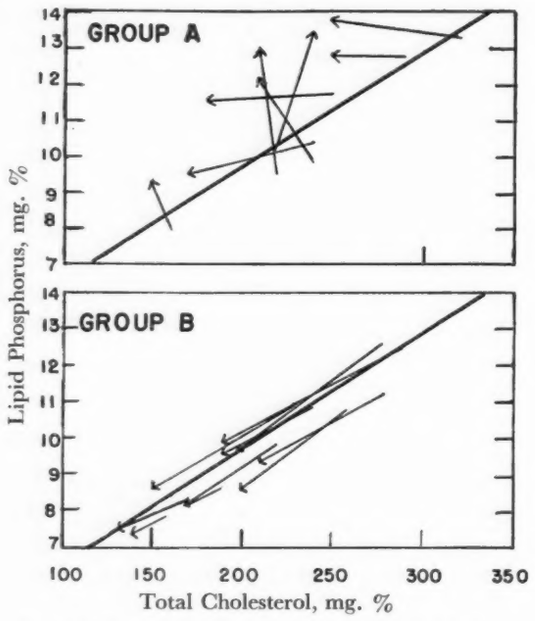

FIG. 13. Concomitant changes in serum lipid phosphorus and total cholesterol on the rice diet in groups A and B (see text). Tail of each arrow represents control period level; head of arrow level obtaining on rice diet in individual patients. Diagonal line represents normal equation of Albrink, Man and Peters:[46] P = 3.3 + .932 C. Note the higher phospholipid levels on rice diet in group A resulting in lower ratios of phospholipid to cholesterol. Group B conforms to the normal relationship.

To be sure, the indications of liver injury in our patients on the rice diet are of such slight degree as to be of equivocal significance. Moreover, it is possible that the positive thymol turbidity tests were evoked by alterations in serum lipid components attributable to the diet itself without necessarily reflecting liver cell damage. It is also possible that the increased sensitivity to dicumarol might be due to failure of vitamin K absorption on the virtually fat-free

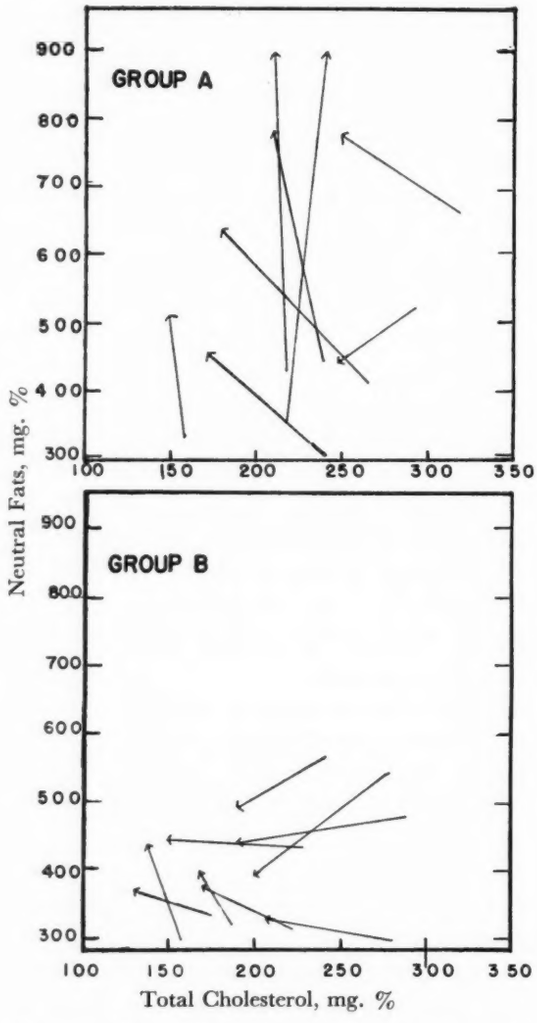

FIG. 14. Concomitant changes in serum neutral fats and total cholesterol on the rice diet in groups A and B (see text). Arrows have same significance as in Figure 13, except that ordinate now represents serum neutral fat in mg. per cent. Distinct elevation of neutral fat level occurred in all but one patient in group A whereas changes were small in group B.

rice diet. Furthermore, the rapidity of the fall in cholesterol esters and in the cholesterol/phospholipid ratio, usually within the first week on the diet, would seem to be inconsistent with the development of fatty liver or other deficiency states, although such alterations may develop in the subsequent course on the diet. The rapidity of these changes (which was in contrast to the usually slower responses of blood pressure, serum electrolytes and nitrogen equilibrium) suggests the possibility of deleterious effects associated with a rapid reduction in hepatic blood flow on the rice diet, analogous to the early decline in renal blood flow. However, measurements of hepatic blood flow by Myers and Murphy[50] in hypertensive patients before and during the rice diet do not appear to indicate any significant reduction.

Supplementation of the rice diet with salt both at the beginning of therapy (five cases) and after a prolonged period on the strict diet (three cases) did not result in any changes in serum cholesterol level or cholesterol ester/total cholesterol ratio which could be distinguished from the effects of the rice diet alone. However, addition of vegetable oil in five cases eliminated the disproportion between free and esterified cholesterol without affecting the total cholesterol level, leading to the postulation that a deficiency of some substance such as an unsaturated fatty acid might be responsible for the lipid disturbances and altered liver function tests occurring in the patients of group A. (Table xv.) Investigating this possibility, it has been found that the feeding of 10 gm. of oleic acid daily to two patients of the group A type partially eliminated the disproportion between free and esterified cholesterol without affecting the level of total cholesterol, lowered the neutral fats of the serum to the level seen in the control period, and reduced the phospholipid level to the extent that the cholesterol/phospholipid ratio became identical with that predicted from the regression equation. Patients of the group B type showed no change in serum total cholesterol, cholesterol ester/total cholesterol ratio, neutral fats or cholesterol/phospholipid ratio when fed the unsaturated fatty acid for ten days.

Reinstitution of the regular diet rapidly reversed all of the serum lipid changes observed on the rice diet. Within a month after discontinuance of the rice diet every one of the ten patients placed on the regular diet had serum levels of cholesterol and cholesterol esters similar to those observed during the control period. In two of the patients whose liver function tests were followed, the abnormalities present on the rice diet disappeared after several weeks on the regular diet. This may be due to restoration of hepatic blood flow analogous to increase in renal blood flow after reinstitution of a regular diet.

Miscellaneous Blood Studies. There were no significant changes in the concentration of *serum proteins* on the rice diet, despite its low protein content. The mean total protein level in the control period was 7.2 gm. per cent, on the rice diet 7.3 gm. per cent; the mean serum albumin value of 4.6 gm. per cent remained unchanged on the rice diet; the mean figure for serum globulins in the control period, 2.7 gm. per cent, was 2.8 gm. per cent on the rice diet. Few individual patients showed appreciable changes in serum protein concentrations in either direction. However, as already pointed out, in view of the contraction of plasma volume on the rice diet a variable decrease in total circulating proteins occurs.

In accordance with Kempner's findings,[3] *serum urea nitrogen* and *non-protein nitrogen* levels uniformly decreased on the rice diet. Our mean figures for serum NPN and urea N in the control period were 40 and 20 mg. per cent, respectively; on the rice diet these levels fell to 31 and 9 mg. per cent, respectively. The largest declines observed were in the fourteen patients with azotemia in excess of the average level. These falls reflect the low nitrogen intake on the rice diet and not improved renal function since, as subsequently pointed out, they occurred in the face of diminished glomerular filtration rate and renal plasma flow.

Fasting *blood sugar* levels were unaffected by the high-carbohydrate rice diet, with one significant exception, Case Mu. C., an overt diabetic whose fasting blood sugar level fell from 220 to 110 mg. per cent on the rice diet despite discontinuance of insulin. A similar interesting indication of increased carbohydrate tolerance on the rice diet was noted in the results of *glucose*

tolerance tests. Of the twenty-nine patients adequately studied in this regard, about half gave glucose tolerance curves on the rice diet which were essentially the same as in the control period; in the remaining patients peak glucose levels on the rice diet were lower than in the control period, the despite appreciable chronic blood loss associated with weekly bleedings for the various blood studies. It should be noted that the rice diet, estimated to provide 11.3 mg. iron daily if prunes and apricots are consumed regularly,[51] is supplemented daily with 0.2 gm. ferrous sulfate.

TABLE XVI

INFLUENCE OF THE RICE DIET ON DISCRETE RENAL FUNCTIONS IN SEVENTEEN PATIENTS WITH HYPERTENSION

(*Figures Corrected to* 1.73 M^2 *Body Surface Area*)

Patient	Surface Area* (sq. M.)	Duration Rice Period (wk.)	Glomerular Filtration Rate (ml./min.)			Renal Plasma Flow (ml./min.)			Filtration Fraction			(T_{mPAH} mg./min.)		
			Control Period	Rice Period	Change Per cent	Control Period	Rice Period	Change Per cent	Control Period	Rice Period	Change Per cent	Control Period	Rice Period	Change Per cent
Males														
H. Col.	1.87	13†	103	89	−13.9	371	367	− 1.1	0.28	0.24	−14.3	81.2	62.7	−22.8
R. G.	1.59	5	42	32	−23.8	118	90	−23.7	0.36	0.35	− 2.8	33.3	13.2	−60.4
C. H.	1.71	6	86	83	− 3.5	336	365	+ 8.6	0.26	0.23	−11.6	70.4	57.8	−17.9
P. K.	1.87	9	85	68	−20.0	350	290	−17.2	0.24	0.23	− 4.2	60.1	48.3	−19.7
B. L.	1.73	12	91	47	−48.4	246	182	−26.0	0.37	0.26	−29.7	37.9	40.9	+ 7.9
B. P.	1.78	7	115	78	−32.2	298	236	−26.3	0.38	0.33	−13.2	71.3	71.1	− 0.3
G. R.	1.75	10	47	31	−34.0	106	97	− 8.5	0.45	0.32	−28.9	22.0	20.7	− 5.9
C. Ro.	1.71	16	63	39	−38.0	243	153	−37.0	0.26	0.25	− 3.8	42.5	27.7	−34.8
F. Sm.	1.83	11	61	56	− 8.2	216	225	+ 4.2	0.29	0.25	−13.8	47.3	32.3	−31.7
Females														
M. Ba.	1.64	11	103	77	−25.2	329	301	− 8.5	0.31	0.26	−16.1	69.9	53.4	−23.6
M. Be.	1.53	6	106	80	−24.5	460	414	−10.0	0.23	0.19	−17.4	90.6	58.0	−36.0
J. Cl.	1.33	4	80	70	−12.5	274	331	+20.8	0.29	0.21	−27.6			
Ma. C.	1.73	9†	88	39	−55.7	221	155	−29.8	0.40	0.25	−37.4			
M. Kn.	1.86	6†	105	80	−24.8	340	334	− 1.7	0.31	0.24	−22.6	61.1	48.7	−20.3
E. M.	1.57	9	77	54	−29.8	166	152	− 8.5	0.46	0.36	−21.8			
H. S.	1.69	6	120	110	− 8.3	434	462	+ 6.5	0.27	0.24	−11.1			
M. Su.	1.73	6	55	35	−36.3	174	135	−22.4	0.32	0.26	−18.8	38.6	36.5	− 5.4
Means		8.6	84	63	−25.8	275	252	−10.6	0.32	0.26	−17.4	55.9	43.9	−20.8
Normal Means‡														
Males			131 ± 21.5			697 ± 135.9			0.19 ± 0.02			Ca. 76.		
Females			117 ± 15.6			594 ± 102.4			0.20 ± 00.3			Ca. 76.		

* Differences in surface area in control and rice diet periods not significant.

† Supplemented with 50 gm. Lonalac daily.

‡ From GOLDRING, W. and CHASIS, H. Hypertension and Hypertensive Disease. New York, 1944. The Commonwealth Fund.

decline more rapid; and in five patients with distinctly diabetic-type response to the glucose tolerance tests, all (including Case Mu. C.) reverted toward normal on the rice diet. These results conform with Kempner's report[3] that diabetics tolerate the rice diet unexpectedly well, often with reduction of insulin requirements.

With regard to effects of the rice diet on the *formed elements of the blood*, repeated blood counts revealed no appreciable change in hemoglobin, hematocrit, erythrocytes or total or differential leukocyte count in the rice diet period as compared with the control period. Blood levels were maintained

Renal Function Studies. Patients with essential hypertension, even in early stages of the disorder and in the absence of any overt indication of renal damage or cardiac failure, frequently show significant reduction in maximal tubular excretory capacity, decrease in effective renal blood flow, more or less diminution of glomerular filtration rate and elevation of the filtration fraction. As Chasis et al.[20] and Weston et al.[52] have demonstrated, these disturbances are, in general, aggravated by the rice diet, particularly in regard to the glomerular filtration rate which was found to be decreased further by 25 to 40 per cent or more in most

cases. Further reduction in renal plasma flow was less consistently observed, the high filtration fraction consequently decreasing. Tubular transport capacity (Tm) for para-aminohippurate fell in somewhat more than half the cases. The rate at which these changes occurred was not clearly established but they seemed to be present two or more weeks after institution of the rice diet. Our own observations are in accord with these findings.

Control period: Table XVI presents our data on glomerular filtration rate (inulin clearance), renal plasma flow (PAH clearance) filtration fraction and Tm_{PAH} in seventeen patients during the control and subsequent rice diet periods. In the control period renal plasma flow was found to be depressed in all subjects (mean: 275 ml./min.). Glomerular filtration rate and PAH transport capacity were below normal in most instances (means: 84 ml./min. and 56 mg./min., respectively). The filtration fraction was elevated in every instance, the highest being 0.46, the mean 0.32.

Rice diet: On the rice diet (Table XVI) the glomerular filtration rate was found to be further depressed in all cases although in three instances the change was very small. The mean decrease was 26 per cent of the control level. In seven patients the reduction in renal plasma flow was greater than 10 per cent of the control value, in one there was an increase of 21 per cent, the remainder showed changes within the range of ± 10 per cent. The mean decline was 10.6 per cent of the control level, which is of borderline significance (D. F. 16, $t = 2.8$, $P = .014$). The disproportionate decrease in glomerular filtration rate resulted in a fall in filtration fraction in all cases, the mean dropping from 0.32 to 0.26. Para-aminohippurate transport capacity was significantly decreased in nine of the thirteen patients studied, being essentially unchanged in the remaining four patients.

The alterations in renal hemodynamics as measured by these tests were not significantly correlated with changes in diastolic blood pressure or serum sodium level occurring on the rice diet. The largest decreases in filtration fraction, however, were observed in patients B. L., G. R., Ma. C., E. M. and J. Cl. who were in fairly severe congestive heart failure in the control period and recompensated on the rice diet. As indicated in Table IX these patients also had relatively large plasma volumes during the control period. Figure 15 indicates the distribution of concomitant changes in plasma volume and filtration fraction, the four points at the upper right representing the patients with initial cardiac failure (plasma volume data not available in Case Ma. C.). There was no correlation of plasma volume changes with alterations in glomerular filtration rate or renal plasma flow alone.

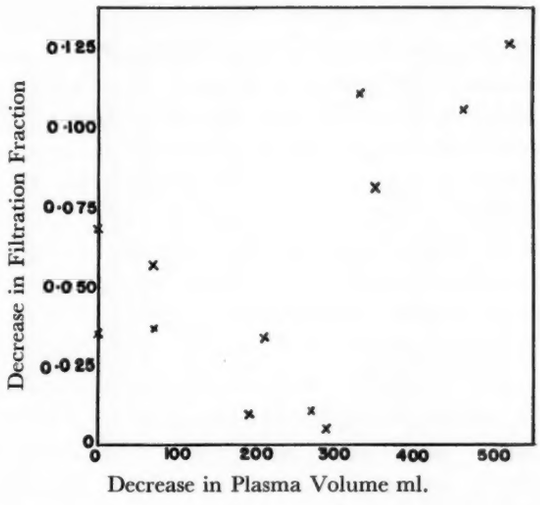

FIG. 15. Scatter graph of relationship between decreases in renal filtration fraction and in plasma volume in welve patients with essential hypertension following rice diet. The four points at upper right represent patients B. L., G. R., E. M. and J. Cl. who had cardiac failure during control period which was controlled on rice diet.

In three patients who had shown characteristic renal function responses to the rice diet (Cases P. K., F. Sm., M. Be.) 3.0 gm. sodium chloride was added daily to the otherwise unmodified rice diet for three, five and six weeks, respectively, and the tests then repeated. Two of these patients (Cases P. K. and F. Sm.) showed further reductions in glomerular filtration rate (-8 per cent and -22 per cent, respec-

tively) and renal plasma flow (−5 per cent and −30 per cent, respectively) with no significant change in Tm_{PAH}; in the third patient (M. Be.) there was a moderate increase toward control levels in all categories. Three of the patients included in Table XVI (Cases H. Col., Ma. C., M. Kn.) were receiving a low-sodium protein supplement to the rice diet in the form of 10 gm. protein as lonalac® and their responses are indistinguishable from the rest. In two patients who had shown typical reductions in renal hemodynamic responses to the unmodified rice regimen (Cases C. Ro. and M. Su.) subsequent addition to the rice diet of 10.5 gm. protein in the form of lonalac® for four and seven weeks, respectively, resulted in no change in the renal function measurements in one instance and insignificant further depression of values in the other; a similar experiment in Case C. Ro. with daily addition of 26 gm. protein as lonalac® for five weeks resulted in an insignificant rise in glomerular filtration rate and renal plasma flow and no change in filtration fraction or Tm_{PAH}. In contrast, two patients (Cases P. K., M. Su.) who had shown characteristic reductions in all measured renal function tests on the rice diet showed return to approximately control levels in all categories when the measurements were repeated five and eight weeks, respectively, following resumption of a regular diet.

Weston et al.[52] found that glomerular filtration rate was significantly decreased (when recalculated as percentage change) by a diet containing 0.5 to 0.8 gm. sodium and 65 gm. protein per day. Renal plasma flow and tubular transport capacity for PAH were not consistently affected. Subsequently on the rice diet further depression of glomerular filtration rate and a drop in renal plasma flow and Tm_{PAH} occurred. In an acute experiment it was shown that infusion of an isotonic solution of human serum albumin was followed by a striking increase in plasma volume and renal plasma flow but relatively little change in glomerular filtration rate. Chasis et al.[20] found that daily addition of 30 gm. sodium chloride to the rice diet resulted in a rise in glomerular filtration rate to approximately control levels. Since there were inconstant small increases in renal plasma flow, the filtration fraction rose in every instance. PAH transport capacity was unaffected by the salt addition. Both Weston et al. and Chasis et al. noted return toward control levels of all renal functions measured after their patients resumed a regular diet.

The available data seem to imply that changes in renal plasma flow, glomerular filtration rate and filtration fraction in patients on the rice diet are associated only in part with changes in plasma volume. Failure of added sodium to affect tubular transfer capacity for PAH also suggests some other deficiency in the rice diet as the factor responsible. Addition to the rice diet of sodium chloride alone in amounts that are small but sufficient in most instances to cause a significant rise in blood pressure will not restore the renal hemodynamics to control figures, although very large salt supplements will do so. Addition of salt-free protein alone in amounts sufficient to constitute fairly adequate protein intake also has little effect. On the other hand, institution of a regular diet restores the measured renal functions to their control levels within a few weeks.

As Kempner[3] points out, blood urea nitrogen levels fall on the rice diet—in his series from a mean of 14.1 mg. per cent to 7.8 mg. per cent, in ours from a mean of 20 mg. per cent to 9 mg. per cent. This is accomplished in the face of diminished urea clearance on the rice diet and reflects the very low nitrogen intake, not improved renal function. Kempner[3] also points out that the low-protein, high-carbohydrate content of the rice diet, which is associated with decreased intake of phosphorus and sulfur, would tend to minimize acidosis due to retention of phosphate and sulfate in patients with severe kidney damage. In such patients, however, the unmodified rice diet imposes the hazard of sodium depletion through salt loss in the urine. The high potassium content of the rice-fruit diet is

another consideration to be taken into account under these circumstances.

The depression of renal hemodynamics produced by the rice diet must be regarded as an unfavorable even if reversible effect. It is not possible from the available data to determine what deleterious results may accrue to the patient or to the disease process. There were no indications in this study of tangible adverse effects on the kidney as revealed by the usual urine and blood examinations.

Nitrogen Balance Studies. One of the most startling and controversial claims made by Kempner[3] is that nitrogen equilibrium may be attained on the low protein intake of the rice diet, at least after a prolonged period of metabolic adjustment and stabilization. This claim was originally based on the extremely low daily urinary nitrogen excretion, which after two months of rice diet Kempner[2] found to average 2.26 gm.; and an *assumed* daily fecal nitrogen output of 0.9 gm. (the daily fecal nitrogen loss in starving man after stabilization), an assumption which ignores the disproportionately high nitrogen content of the bulky stools in cereal-rich diets.[53] Peschel and Peschel,[54] working in Kempner's clinic, subsequently presented more convincing evidence in support of this claim by their nitrogen balance studies in eleven hypertensive patients who had been on the rice diet for a mean of eighty-nine days. On a mean daily nitrogen intake of 4.37 gm., the mean total nitrogen output was found to be 4.12 gm., of which 2.57 gm. appeared in the urine and 1.55 gm. in the stools, for a mean net positive balance of 0.25 gm. nitrogen per day. Of twelve balance studies made in eleven patients, in five the balance was slightly negative, in seven it was slightly positive.

Schwartz and Merlis[55] fed a rice diet providing only 2.63 gm. nitrogen per day to six normotensive patients for eight days (after four days on a nitrogen depletion diet) and noted an average daily negative nitrogen balance of 3.22 gm. One hypertensive patient studied after ninety days on a rice diet still showed a negative nitrogen balance of 2.67 gm. per day. Currens et al.[56] reported a negative nitrogen balance of 5 gm. per day during the first week on the rice diet in one hypertensive patient and a daily negative balance of 1 gm. in a second patient after three months on the rice diet.

TABLE XVII
NITROGEN BALANCE DATA IN EIGHT PATIENTS WITH ESSENTIAL HYPERTENSION ON THE RICE DIET FOR VARYING PERIODS

Patient	Week of Rice Diet	Nitrogen Gm./Day					Weight Change (kg.)
		Intake	Urinary Output	Fecal Output	Total Output	Balance	
G. R.	1	4.12	6.20	2.09	8.29	−4.17	−1.5
	2	5.14	4.54	2.34	6.88	−1.74	−0.6
	3	5.45	4.94	1.68	6.62	−1.17	−0.8
	4	4.92	4.45	1.94	6.39	−1.47	−0.3
D. B.	3	4.69	3.47	1.24	4.71	−0.02	−0.9
	4	4.78	3.07	1.12	4.19	+0.59	0.0
C. A.	5	4.12	4.00	2.06	6.06	−1.94	−0.2
	6	5.14	3.83	1.89	5.72	−0.58	0.0
	7	5.45	4.35	2.03	6.38	−0.93	+0.1
	8	4.92	3.69	1.99	5.68	−0.76	0.0
R. C.	4	4.89	2.99	0.99	3.98	+0.91	−0.4
	5	4.90	2.63	1.46	4.09	+0.81	+0.3
	12	4.88	2.37	1.66	4.03	+0.85	+0.3
A. A.	7	5.25	2.60	2.12	4.72	+0.53	−0.3
	8	5.08	2.49	1.80	4.29	+0.79	0.0
F. H.	16	4.44	2.87	1.63	4.50	−0.06	0.0
	17	4.18	3.19	1.45	4.64	−0.46	+0.3
S. N.	16	4.31	2.62	2.33	4.95	−0.64	−0.9
	17	4.18	2.58	1.96	4.54	−0.36	−0.2
F. Sm.	13	4.94	3.12	2.37	5.49	−0.55	−1.2
	14	5.14	2.98	1.89	4.87	+0.27	0.0
	35	4.90	2.03	1.89	3.92	+0.98	−0.6

Our own studies confirm the rapid decline of urinary nitrogen excretion in the initial weeks of the rice diet, as illustrated by the results in Case W. H. (Fig. 10.) On a mean daily nitrogen intake of 4.9 gm. the urinary nitrogen excretion fell from about 12 gm. to 5 gm. per day in the first three days and thereafter gradually diminished to levels of about 4 gm. per day by the end of the third rice diet week. The rate of decrease in urinary nitrogen and the equilibrium levels reached varied from patient to patient but, as shown in Table XVII, daily urinary outputs of 2 to 3 gm. nitrogen were the rule after the first month or two on the rice diet. Figure 10 also illustrates the moderate decline in urinary total creatinine output, from 1,300 to 1,100 mg. per day. Urinary uric acid excretion fell promptly on the rice

diet from control period levels of 600 to 700 mg. per day to 400 to 500 mg. per day. Uric acid/creatinine ratios dropped from control period values of about 0.50 to 0.40.

The results of nitrogen balance studies in eight patients after varying periods of time on the rice diet are summarized in Table XVII. Case G. R. illustrates the markedly negative nitrogen balance invariably present in the initial weeks. As the diet is continued the negative balance becomes less marked. In some instances virtual equilibrium apparently is reached, in others nitrogen losses of greater or lesser degree continue indefinitely, in some instances slightly positive balance seems to be achieved. Much depends upon whether or not the patient continues to consume the full quota of rice, which in routine management often is not the case. An important additional factor is the frequency and bulk of the stools, which contain a disproportionately large fraction of the total nitrogen excretion.

In these nitrogen balance studies no allowance has been made for the requirements of "adult growth" and for dermal nitrogen losses, which Mitchell and Hamilton[57] estimate to be about 0.4 gm. daily under non-sweating conditions but may be less on the low nitrogen intake of the rice diet. When these requirements are taken into account, it is unlikely that true nitrogen equilibrium often is achieved on the unmodified rice regimen even under the most favorable circumstances. The nitrogen loss under optimal conditions is small however in relation, for example, to losses regularly incurred in fever and debilitating illness and should not be regarded as a major deterrent to the rice diet. This holds particularly, of course, if the body weight is maintained at a reasonably constant level, even if this may be due in part to replacement of lean body mass by fat. Nevertheless, the rice diet should be supplemented sooner or later with sources of low-salt protein other than rice. We have found that daily addition of lonalac® in quantities equivalent to 1.6 gm. nitrogen is sufficient to produce unequivocally positive nitrogen balance in most instances and that this addition to the rice diet does not vitiate its effectiveness. More work along these lines is in progress.

COMMENTS

Significance of Effects of Rice Diet on Hypertension. There has been some tendency in recent years to minimize the significance of elevated blood pressure in essential hypertension as only one manifestation of a complex syndrome and a manifestation of perhaps lesser clinical significance. This is justifiable conservatism and a healthy reaction to indiscriminate overemphasis of blood pressure levels, disregard of the errors of indirect measurement,[58] inappreciation of the large range of spontaneous variation,[10,59,60] neglect of the importance of the rate of progression of the hypertensive state[61] and uncertainties as to the boundary between normotensive and hypertensive levels.[62] Nevertheless, indirect measurement, if properly performed, roughly approximates the results of direct intra-arterial recording,[63,64] and blood pressure readings can be made under basal conditions in a controlled environment and over a prolonged period of stabilization. These qualifications appear to have been met in the present study and it would seem valid to conclude that the fall in basal blood pressure observed in many of our patients on the rice diet was greater and more consistent than could justifiably be ascribed to spontaneous variation, effects of hospitalization *per se*, suggestion or psychotherapy. We therefore concur in Kempner's opinion that the rice regimen, if followed with sufficient attention to detail, specifically reduces the blood pressure in a significant proportion of patients with severe essential hypertension.

It would appear that the effects of the rice diet in respect to hypertension exceed those hitherto obtained, under controlled conditions at any rate, in the treatment of severe essential hypertension by any method short of sympathectomy. So far as now ascertained the response in blood pressure is due chiefly to the very low sodium content of the rice diet. Rigid restriction of

sodium, as advocated particularly by Allen and Kempner, would therefore seem to be an important principle in the dietary management of at least the comparatively small proportion of patients with essential hypertension who require more than reassurance, rest, weight reduction, sedation or rudimentary psychotherapy.

It is quite clear, however, that the critical tolerance level of sodium intake, with respect to effects on blood pressure in essential hypertension, is extremely low in patients in the advanced stages of the disorder, of a much lower order of magnitude than is effective in most patients with congestive failure due to other causes. In fact, it is so low that it has not yet been convincingly demonstrated that effective dietary sodium levels can be achieved by diets other than the rice diet or equivalent extremely restricted regimens. Such diets, however, can be maintained sufficiently free of sodium only with great difficulty even in hospitals with special facilities; and, of course, with even greater difficulty in clinics and in the home, particularly if patients must depend in part upon casual restaurant preparation of food. Needless to say, the stringent dietary restrictions impose such great hardships upon the patients that only a minority can sustain a sufficiently low-sodium intake long enough to obtain persistently salutary effects. With resumption of a normal diet, or of the usual "low salt" diets, blood pressure levels rapidly return to pretreatment levels.

These limitations of rice diet therapy are exemplified by our own experience with recurrence of hypertensive levels upon resumption of a regular diet or a more diversified low-sodium diet in the hospital or after discharge for continued regulation in the home. While still in the hospital thirteen of the fifty patients reported upon here, after terminating their period on the strict or modified rice diet, resumed the regular control period diet. In ten the blood pressure rose appreciably. The rate of increase varied considerably, in some cases the new level being reached in the first or second week after the diet change while in others there was a slowly progressive increase of blood pressure over a period of several months. In three patients no significant rise in blood pressure occurred over the protracted period of hospitalization. The mean basal blood pressure, which was 157/92 for the thirteen cases at the end of the rice diet period, rose after varying periods on the regular diet to 189/106, a change of +32/+14 mm. Hg. It is interesting to note that the mean basal blood pressure at the end of the initial control period for these patients was 188/110 mm. Hg.

In most other respects also there was a return to the status existing in the control period. The clinical findings and symptoms of nine patients, however, remained essentially unchanged for many months after return to a regular diet. Two patients became worse, one with progressive cardiac decompensation, the other entering the malignant stage of hypertension. Two patients died in the hospital, one of cerebral vascular accident, the other in uremia. In general, while the symptomatic benefits of the rice diet may persist, objective evidences of improvement more or less rapidly revert to the pretreatment status upon resumption of a regular diet.

Thirty-two patients have been followed in an outpatient clinic established for this purpose, after discharge from the hospital upon completion of the rice diet period. In general an attempt was made to keep the patients on the rice diet, appropriately modified, as long as possible. When this proved no longer feasible a low-sodium regimen of the conventional type, or in some cases a regular diet, was instituted. Observations made over a follow-up period ranging from a few weeks to twenty months, mean duration about one year, are available.

At the time of analysis one-half of the group was on a modified rice diet, with varying degrees of adherence (excessive cheating excluded), and one-half was on low-sodium or regular diets for the greater part or all of the follow-up period. Of the sixteen patients on the modified rice diet fourteen had blood pressure levels appreciably higher than at the end of hospitalization; in two cases the blood pressure remained essentially unchanged. The average blood pressure at the end of the follow-up period was 204/122, as compared with 171/89 before discharge from the hospital, an increase of +33/+33. Ten patients had no change in symptoms or clinical condition since discharge from the hospital, most of them being relatively well. Three patients had

noted recurrence of symptoms of congestive failure or headaches. Three patients died, one of bleeding peptic ulcer, one an accidental death, the third of unknown causes.

All but one of the sixteen patients on low-sodium and regular diets showed an appreciable rise in blood pressure after discharge. The average final blood pressure was 210/123, an increase of +42/+28 above 168/95, the basal blood pressure in the last week of hospitalization. In this group the clinical condition of six patients remained unchanged; eight patients became worse, developing headaches or congestive failure or angina; two patients died, one of presumed myocardial infarction, the other of unknown causes.

The following tabulation summarizes the results of our follow-up observations to date, representing periods of one to twenty months (mean about one year) since termination of the rice diet period on this Service:

Total number of patients		50
Home on modified rice diets		16
Recurrence of hypertensive levels	14	
Persistence of lowered blood pressure	2	
Recurrence of symptoms	3	
No recurrence of important symptoms	10	
Dead	3	
Home on low-sodium or regular diets		16
Recurrence of hypertensive levels	15	
Persistence of lowered blood pressure	1	
Recurrence of symptoms	8	
No recurrence of important symptoms	6	
Dead	2	
In hospital or recently discharged		6
Lost to follow-up		3
Dead		9
Cerebrovascular accident (Cases S. D., Y. R.*)	2	
Uremia (Cases T. Mc.,* G. K.)	2	
Presumed myocardial infarction (Case An. Wa.)	1	
Accidental causes (Case H. Col.)	1	
Unknown causes (Cases H. O., G. R.)	2	

* These two patients, previously discussed, died while on the unmodified rice diet in the hospital.

It will be noted that the final blood pressures in the groups on the rice and less restricted diets, 204/122 and 210/123, respectively, are similar to the mean initial acceptance blood pressure of 227/132 for the entire group of fifty cases. Of course a large part of the increase over final hospital blood pressures may be ascribed to the non-basal conditions in the clinic, although familiarity with the physicians was a constant factor. It would appear that little or no decrease in blood pressure was sustained more than a few weeks beyond the end of hospitalization regardless of the diet subsequently employed. The smaller incidence of recurrence of symptoms in the group on modified rice diets may be entirely attributable to the fact that this group consisted of the more cooperative and intelligent patients or those better situated for preparation of a special diet.

This experience, like that of many others, leads us to believe that while the Kempner rice regimen has an important place in the treatment of severe essential hypertension, in its present form it is not a practical means of sustained management in most cases. To be sure, our patients fall for the most part in the less favored economic group often without adequate home facilities for preparation of the rice diet and dependent for subsistence upon restaurant meals. Kempner has demonstrated that under more favorable conditions the rice regimen, ultimately liberalized somewhat within individual tolerances, can be maintained effectively for several years, with persistent lowering of blood pressure and amelioration of complications in a sizable number of patients. But what proportion of his patients who initiate the rice regimen are able to maintain it long enough to lengthen substantially the life span of patients in advanced stages of essential hypertension has not yet been made clear and the follow-up period is still comparatively short. It seems evident that the Kempner rice regimen is more than merely palliative but appraisal of the long-term effects is not yet possible with the critique afforded, for example, by the reports of five-year follow-up studies of the response to sympathectomy.

It is probable that the unmodified Kempner rice regimen is unnecessarily restrictive in some respects, as suggested by the efficacy of certain modifications; however, additions to the diet, such as thoroughly boiled meats, incur the risk of exceeding the critical tolerance level of the hypertensive patient for sodium. It is also quite possible that in some patients with essential hypertension, especially those in earlier phases of the disorder, the critical level of sodium intake is higher, within the range of various well rounded and palatable

diets alleged to have sodium chloride contents less than 1.0 gm. It has not been satisfactorily demonstrated as yet that the lowering of blood pressure obtained with such diets is greater and more frequent than can be ascribed to spontaneous variation, restricted activity, loss of weight, reassurance and psychotherapy.

The effects of rigid salt restriction upon hypertension are of the greatest interest from the point of view of the pathogenesis of essential hypertension. It is improbable that the rice diet strikes at the primary causes of essential hypertension; more likely secondary pathways are interrupted but the mechanisms affected are still wholly obscure. That the effects may be mediated through the adrenal glands is an attractive hypothesis but one as yet based very largely on speculation.

Significance of Effects of the Rice Diet in Relation to Relief of Congestive Failure. It is pertinent to inquire whether the benefits derived from the rice diet are not largely due to relief of the manifestations of cardiac failure, this being achieved by unnecessarily onerous and restrictive measures when more conventional therapy, imposing less hardship upon the patient, might give equivalent results. There can be little question that a large component of the improvement observed in many advanced cases of essential hypertension, particularly those with frank congestive failure, is attributable to recompensation on the rice diet. This is apparent in the early relief of symptoms and signs of overt heart failure, the frequently impressive diuresis and weight loss in the first week of the rice regimen and the decreased venous pressure and circulation time. It has already been indicated that the reduction in heart size which may occur in the early weeks of the rice diet is associated in our experience with diminished plasma volume and is construed as chiefly a manifestation of recompensation with decreased cardiac dilatation. Not infrequently in our experience recompensation occurred on the rice diet in patients who had shown only tolerable response to digitalis, mercurial diuretics and ordinary low salt diets for years elsewhere and during the weeks or months on the control period on this Service. It would appear that while most patients with hypertensive congestive failure regain compensation with the modest restriction of sodium imposed by the usual low-sodium diets as ordinarily dispensed, for optimal results some require the extremely low sodium intake possible only with the rice regimen or similar drastically restrictive diets.

There is every indication, however, that the effects of the rice diet cannot be ascribed solely to relief of congestive failure. Fall in blood pressure is not a characteristic of cardiac recompensation which ordinarily is followed by some rise in blood pressure levels if there is any change at all. The striking improvement in retinopathy, insofar as it can be taken to reflect general regression of the small artery changes associated with hypertension, is not the usual accompaniment of relief of congestive failure. The same may be said of many of the other responses to the rice diet described by Kempner and corroborated in this study.

Significance of Effects of Rice Diet on Serum Lipids in Relation to Arteriosclerosis. It has already been pointed out that the metabolic and clinical effects of the rice diet on lipid metabolism are of special interest since the diet contains no cholesterol, practically no fat and minimal amounts of protein, thus constituting an extreme form of dietary management of the most frequent and serious accompaniment of essential hypertension—arteriosclerosis. In this connection it is important to recognize that many patients with essential hypertension appear to have an intrinsic disturbance in lipid metabolism. As the data indicate, this metabolic error may be apparent as an abnormally high serum total cholesterol level which moreover shows fluctuations, often cyclical, that distinctly exceed the limits of variation in the normal individual. It would therefore appear that any group of patients with essential hypertension is likely to include a large proportion of

individuals (some two-thirds of our small series) who have the chemical stigmata of coronary arteriosclerosis even though arteriosclerosis may not yet be apparent clinically, electrocardiographically or roentgenographically. This is in accord, of course, with clinical experience in essential hypertension that there is a high incidence of late complications due to coronary, cerebral and renal arteriosclerosis. It would further appear that if restrictive diets can be shown to have any beneficial effects on the serum lipids, their use in one or another form should receive serious consideration in the management of at least those patients with essential hypertension who have chemical stigmata suggesting a special predisposition to arteriosclerosis. Finally, and particularly germane to this discussion, since serum cholesterol levels are prone to inordinately large fluctuation in hypertensive patients it is important in appraising the effects of the rice diet to obtain cholesterol determinations in numbers sufficient for proper orientation both before and during treatment. This appears not to have been done previously.

With regard to the effects of the rice diet on serum total cholesterol levels, our data show the distinct fall found by Kempner and Starke, although in our small series the mean decline was less, 40 mg. per cent. This would appear to be a highly desirable response to the diet and one which in our series evidently is not associated with starvation or weight loss. It is not yet clear, however, whether a fall in serum total cholesterol of this magnitude has any significant prophylactic or therapeutic effect on the course of the disease, particularly over the relatively short period in which the unmodified rice diet can be maintained in most patients. Moreover, since the fall in serum total cholesterol very largely involves the cholesterol ester fraction, whatever favorable result may accrue in respect to arteriosclerosis may be at the expense of impairment of hepatic function. It is not yet clear whether the disturbance in hepatic esterification mechanisms is attributable to intrinsic parenchymal damage, to retardation of metabolic processes in the liver associated with reduction in hepatic blood flow, to both or to other factors. Judging from the results of other hepatic function tests made, the liver injury incurred, if any, is of slight degree and readily reversible upon resumption of a regular diet.

Of considerable interest is the observation that while the serum cholesterol levels fall on the rice diet, they do not drop below the normal range. This is a striking indication of the large capacity in man for endogenous synthesis of cholesterol from acetate derived from carbohydrate, the only source available in quantity in the rice diet.

With regard to the decline in cholesterol/phospholipid ratio observed in seventeen of eighteen patients on the rice diet, this would also appear to be a highly desirable response. Cholesterol in the serum is not in simple molecular solution but is stabilized by combinations in the form of cholesterol–phospholipid–proteins, notably the β- and α-lipoproteins.[65,66] As suggested by Kendall,[67] an increase in the cholesterol content of the serum beyond the capacity of the proteins to combine with it may lead to the formation of cholesterol–phospholipid complexes, such as described by Gofman,[68,69] and eventually to unstable cholesterol emulsions if insufficient phospholipid is present, i.e., if the cholesterol/phospholipid ratio is sufficiently high. The causal relationship of such disturbances to the pathogenesis of arteriosclerosis is still hypothetical but lowering of the cholesterol/phospholipid ratio would seem from present indications[42,43,70] to be an advantageous objective in disorders associated with hypercholesterolemia and a high incidence of arteriosclerosis. Accomplishment of this end in some of our hypertensive patients on the rice diet is, however, subject to reservations similar to those expressed in connection with the lowering of serum total cholesterol. While the change in cholesterol/phospholipid ratio is in the desired direction, it is not now possible to state whether it is of sufficient magnitude and can be sufficiently

maintained to exert any significant effect on the course of the disease. Moreover, the lowered ratio may well be an expression of altered metabolic activity in the liver and perhaps another reflection of hepatic injury.

SUMMARY AND CONCLUSIONS

1. The results of a two-year investigation of the Kempner rice regimen in fifty patients with advanced essential hypertension are reported. The study was made under controlled conditions: All patients were hospitalized throughout the period of observation, the rice diet was prepared in a special kitchen with proper safeguards for low sodium content, the patients were first studied in a fore-period adequate for stabilization (mean duration 10.1 weeks), and then for a mean period of 10.5 weeks on the unmodified rice regimen.

2. Our results in the relatively short period of observation on the rice diet corroborate in most essentials the reports by Kempner in respect to symptomatology, hypertension, retinopathy, electrocardiographic changes, cardiac enlargement, electrolyte and nitrogen metabolism, and serum total cholesterol. Unfavorable but reversible effects on discrete renal and hepatic functions were noted. Additional data on metabolic and clinical effects of the unmodified rice diet are recorded.

3. The effects of systematic addition of sodium chloride to the rice diet, without knowledge of the patient, corroborate the view that the extremely low sodium content of the rice diet is the most significant factor in reduction of elevated blood pressure levels. Addition of salt-poor protein and of fat suggest that the rice diet may be unnecessarily restrictive in regard to protein and perhaps in other respects. More controlled study along these lines is needed.

4. Rigid restriction of sodium, as advocated particularly by Allen and Kempner, would seem to be an important principle in the dietary management of at least the comparatively small proportion of subjects with essential hypertension who require more than reassurance, weight reduction or mild sedation. Effective application of this principle for sustained treatment, however, is exceedingly difficult because the critical tolerance level of sodium intake with respect to hypertension appears to be extremely low, at least in many patients in progressive and advanced stages of essential hypertension, and sodium intake above the critical level causes more or less prompt return of hypertensive manifestations.

5. Protracted effective maintenance of the Kempner regimen in its present form imposes such hardship upon the patient and so much difficulty in control as to make it virtually impracticable for general use. The effects of less restrictive low-salt diets have not yet been studied on a sufficiently large scale and under sufficiently controlled conditions to determine whether or not they have more than psychotherapeutic value.

6. The results of sodium restriction in essential hypertension would seem to be promising enough to justify further extensive exploration. Among the points that should be clarified are (1) the extent to which the Kempner rice regimen may be diversified without serious compromise of its effectiveness; (2) the limits of sodium tolerance levels with respect to elevated blood pressure level in patients with essential hypertension, especially those with less severe manifestations than considered in this report; (3) the effectiveness, under controlled conditions, of low-sodium diets more diversified and palatable than the rice diet; (4) the indications for restrictive dietary management of essential hypertension in relation to sympathectomy.

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Effect of the Rice Diet on the Serum Cholesterol Fractions of 154 Patients with Hypertensive Vascular Disease*

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EITHER hypercholesterolemia or hypertensive vascular disease or a combination of both seems to play an important role in the development of atherosclerosis. Close association between atherosclerosis and a high concentration of cholesterol in the serum has been observed in patients with diabetes mellitus,[1–4] chronic nephritis,[5,6] hypothyroidism[7–9] and xanthomatosis.[10–12] High serum cholesterol concentrations have also been found in patients with coronary artery disease,[13,14] peripheral arteriosclerosis,[15] generalized arteriosclerosis,[16] exudative vascular retinopathy[17] and hypertensive vascular disease.[18–20]

Numerous studies have been made to answer the question whether or not the serum cholesterol concentration can be altered by diet. In fasting, the serum cholesterol rises in men and in animals (swine, cat and guinea pig).[21] Total and esterified cholesterol increase in a roughly parallel way. Following the ingestion of food at the termination of the fast, the cholesterol bound as ester drops more rapidly than does the total cholesterol.

Slightly higher cholesterol values were obtained in four normal women when the diet contained 3.1 gm. of cholesterol per day than when 0.77 gm. of cholesterol per day was given.[22] The values were higher when the cholesterol was administered in egg yolks than in butter containing pure cholesterol. Total serum cholesterol figures as high as 315 mg. per 100 cc. and 600 mg. per 100 cc. were reported in two Arctic explorers who ate a diet very high in fat for twelve months.[23] The serum cholesterol values dropped to 218 mg. per 100 cc. and 200 mg. per 100 cc. when, after their return to a temperate climate, they resumed a diet with a lower fat content.

When egg yolk powder (100 gm. per day) was added to a constant 2,500 calorie diet given to eight patients with arthritis, the serum cholesterol increased by 50 to 170 mg. per 100 cc. within six to ten weeks. In two nephritics who were treated in the same way the serum cholesterol increased by 104 and 218 mg.[24] Rabinowitch[25] found that in diabetics, with the institution of a high-carbohydrate, low-calorie diet, an immediate and sustained decrease of plasma cholesterol occurred.

Steiner[26] reported: "Nine individuals were placed on diets high or low in fat and cholesterol. They were first given a diet containing 300 Gm. of fat for six weeks and then without interruption placed on a diet containing less than 50 Gm. of fat. In five of the nine patients there was no increase in total serum cholesterol during the period of high fat feeding. In four cases a slight rise seemed to occur. Three of the patients subsequently were placed on the high fat diet for a second period but this time 10 Gm. of cholesterol in 200 cc. of milk was added to the regimen. No significant change resulted in the serum cholesterol levels. The serum cholesterol levels of the patients on a low fat diet were no different from those observed during the control period."

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Keys[27] found that young men, aged eighteen to twenty-five, whose diet contained 1.49 gm. of cholesterol per week had the same serum cholesterol concentration as those whose diet contained 4.20 gm. Average serum cholesterol values ranged between 165 and 184 mg. In older men aged forty-five to fifty-five the average range was between 242 and 258 mg. There was no difference in the serum cholesterol concentration when the diet contained 1.62 gm. or 4.81 gm. of cholesterol per week. Keys summarized, "Neither in the younger nor older men is there any relation between blood cholesterol and the habitual intake of cholesterol, in spite of the fact that the differences in the latter are large."

Kempner examined the effect of the rice diet on the serum cholesterol concentration of patients with kidney disease or hypertensive vascular disease. The rice diet contains in 2,000 calories not more than 5 gm. of fat and about 20 gm. of protein derived from rice and fruit, and not more than 200 mg. of chloride and 150 mg. of sodium. A marked reduction of the total[28–30] and esterified[30] cholesterol concentration in the serum of more than 90 per cent of the patients was found.

This paper reports 401 determinations of free and esterified serum cholesterol on 154 patients with hypertensive vascular disease. The effect of the rice diet on the cholesterol fractions was studied after varying periods of time.

METHODS

Total serum cholesterol was determined according to Bloor's method[31] adapted to the photoelectric colorimeter. The Sobel and Mayer[32] modification of the Schoenheimer-Sperry method for free cholesterol was used. All determinations were made in duplicate.

One hundred five patients were male; forty-nine patients were female. Twenty-nine of the women were fifty years of age or older. The ages of the patients ranged from nineteen to seventy years, average fifty-one years.

All patients with nephritis or with fasting blood sugar levels above 115 mg. per 100 cc. were excluded. None of the patients had clinical thyroid disease. Basal metabolic rate was obtained on sixty-nine patients. In fifty-five of these, values were between +15 per cent and −15 per cent of normal. Six had a basal metabolic rate higher than +15 per cent, average +20%; the average total cholesterol of these patients before treatment was 300 mg. per 100 cc. of serum. Eight patients had a basal metabolic rate lower than −15 per cent, average −21 per cent; the average total cholesterol of these patients before treatment was 317 mg. per 100 cc. of serum.

One hundred twenty-two of the 154 patients had cardiac involvement at the time they were first seen. Any one or more of the following is taken as evidence of cardiac involvement: radiologic report of cardiac enlargement, inversion of T_1 or diphasic T_1 in the electrocardiogram, bundle branch block, auricular fibrillation or myocardial infarction.

Fifty-six patients had hemorrhagic vascular retinopathy. Fifty-five had exudative vascular retinopathy. Ten had papilledema. Fifty-six patients had renal involvement. A PSP excretion of less than 50 per cent in two hours, a blood non-protein nitrogen higher than 45 mg. per 100 cc., or proteinuria of more than 0.5 gm. per L. is taken here as evidence of renal involvement. Twenty-one patients had had cerebrovascular accidents or convulsions. Arcus senilis was noted in thirty-four patients.

RESULTS

The mean total cholesterol of 154 patients before treatment was 272 ± 4.4 mg. per 100 cc. of serum. The mean free cholesterol of all 154 patients before treatment was 76.2 ± 1.5 mg. per 100 cc. of serum. The mean esterified cholesterol before treatment was 195.8 ± 3.2 mg. per 100 cc. of serum. The mean ratio of free to total cholesterol before treatment was 28.0 ± 0.25 per cent. One hundred twenty-five patients had a serum cholesterol of more than 220 mg. per 100 cc. of serum before treatment, average 289 mg. per 100 cc. Twenty-nine patients had a serum cholesterol of 220 mg. per 100 cc. or less before treatment, average 199 mg. per 100 cc.

Total and free serum cholesterol was determined in the serum of thirty-six normal individuals whose ages ranged from seventeen to forty-seven years. The mean total

cholesterol was 198 ± 6.2 mg. per 100 cc. of serum. The mean free cholesterol was 54.9 ± 2.1 mg. per 100 cc. of serum. The mean ratio of free to total cholesterol was 27.7 ± 0.6 per cent.

Table I summarizes the changes in total and free cholesterol and in the ratio of free to total cholesterol over varying periods of time. The results of the calculations for significance are shown.

It appears from these data that the total cholesterol decreases rapidly and that the decrease is maintained when the patient follows the rice diet, that the free cholesterol decreases at a slower rate than does the total cholesterol so that the ratio of free to total cholesterol rises accordingly.

However, there is a difference in the rate of decrease in free cholesterol between those patients who initially had hypercholesterolemia and those whose initial total cholesterol was normal. In the patients who had an initial total cholesterol of 220 mg. or less per 100 cc. of serum the ratio of free to total cholesterol did not change. In those patients who had an initial total cholesterol of 221 mg. or more per 100 cc. of serum there was a definite rise in the ratio of free to total cholesterol. (Table II.)

TABLE I

AVERAGE CHANGES IN THE SERUM CHOLESTEROL FRACTIONS AFTER VARIOUS PERIODS OF RICE DIET

	Time in Days	No. of Observations	Mean Serum Cholesterol (mg./100 cc.)		Average Change	Standard Error	t Value for Mean Difference
			Before Treatment	After Treatment			
Total Cholesterol	5–30	60	270 ± 7.9	209 ± 6.2	−61	4.76	12.82
	31–60	80	271 ± 6.1	212 ± 5.9	−59	4.81	12.27
	61–120	73	271 ± 7.0	202 ± 5.8	−69	4.60	15.00
	121–240	34	272 ± 8.0	191 ± 7.2	−81	7.04	11.51
Free Cholesterol	5–30	60	77.2 ± 2.7	64.1 ± 2.4	−13.1	1.57	8.34
	31–60	80	75.7 ± 2.2	64.2 ± 2.1	−11.5	1.81	6.35
	61–120	73	75.6 ± 2.3	59.7 ± 1.8	−15.9	1.56	10.19
	121–240	34	76.7 ± 2.9	55.5 ± 2.2	−21.2	2.60	8.15

	Time in Days	No. of Observations	Mean (Free Cholesterol × 100) / (Total Cholesterol)		Average Change	Standard Error	t Value for Mean Difference
			Before Treatment	After Treatment			
Ratio	5–30	60	28.5 ± 0.4	30.4 ± 0.4	+1.9	.47	4.04
	31–60	80	28.0 ± 0.4	30.2 ± 0.4	+2.2	.47	4.68
	61–120	73	28.0 ± 0.3	29.7 ± 0.4	+1.7	.50	3.40
	121–240	34	28.2 ± 0.8	29.0 ± 0.4	+0.8	.84	0.95

COMMENT

We do not know all the sources from which cholesterol is derived. It has been shown that cholesterol can be synthesized[33–35] and destroyed[35] in the animal body. Bloch, Borek and Rittenberg[36] found with the Warburg apparatus that intact liver cells under

aerobic conditions produced cholesterol from acetate containing D_2O and C^{13}. Cholesterol can also be synthesized from acetone.

We do not know the mechanism by which the normal cholesterol level in the serum is maintained and why, in the process of aging and in certain diseases, the serum concentration rises. Neither do we know under what conditions hypercholesterolemia causes atherosclerosis.

Further studies will be needed to show why hypercholesterolemia is reduced by the rice diet. It may be due to the low fat or to the low cholesterol content of the diet, or to both. The low protein content of the diet may be of importance. The change in fluid balance, or the low sodium or low chloride content, or the relative alkalinity of the diet may possibly play a role. The slight but definite rise in the ratio of free to total cholesterol on the rice diet calls attention to the liver. There could be decreased blood flow through the liver, decreased excretion of free cholesterol by the liver or decreased production of cholesterol or impairment of esterification.

It is known that feeding of cholesterol causes hypercholesterolemia and atherosclerosis in rabbits.[37–39] Atherosclerosis which sometimes is found "spontaneously" in chickens can be accelerated by cholesterol feeding.[40] Recently Steiner and Kendall[41] have produced hypercholesterolemia and atherosclerosis in dogs by combined feeding of thiouracil and cholesterol. McMeans and Klotz[42] have found regression of the fatty streaks in the arteries of rabbits when the cholesterol was removed from the diet. A low fat diet can retard atherosclerosis in the chicken.[43] Leary[44] has stated that cholesterol deposits in the atheromatous lesions in man may undergo lysis. Wilens[45] has observed a relative absence of atherosclerosis in persons dying of wasting diseases and concludes that "significant resorption of previously formed atheromatous lesions may occur during periods of marked weight loss."

So far there are no figures available which show to what extent lowering of the serum concentration of free and esterified cholesterol in man prevents, retards or arrests atherosclerosis or causes a regression of lesions already present. However, of all the diets used in the treatment of hypertensive vascular disease the rice diet is the lowest in fat and in cholesterol, and has reduced hypercholesterolemia in 98.4 per cent of the 125 patients whose initial total serum cholesterol was more than 220 mg. per 100 cc. In eighty-two of these patients (65.6 per cent) the serum cholesterol fell to normal values (220 mg. per 100 cc. or less).

TABLE II

EFFECT OF RICE DIET ON SERUM CHOLESTEROL FRACTIONS IN TWENTY-NINE PATIENTS WITH AN INITIAL "NORMAL" CHOLESTEROL CONCENTRATION AND 125 PATIENTS WITH AN INITIAL CHOLESTEROL LEVEL ABOVE "NORMAL"

Initial Total Cholesterol (mg. per 100 cc. of serum)	150–220 mg.	221–463 mg.	150–463 mg.
No. of Patients	29	125	154
Total Cholesterol (mg. per 100 cc. of serum)			
Before treatment	199 ± 3.17	289 ± 4.07	272 ± 4.41
After treatment	166 ± 4.85	209 ± 3.99	201 ± 3.63
Free Cholesterol (mg. per 100 cc. of serum)			
Before treatment	57.2 ± 1.76	80.6 ± 1.56	76.2 ± 1.50
After treatment	47.4 ± 1.55	62.5 ± 1.39	59.7 ± 1.26
Ratio $\frac{(\text{Free Cholesterol} \times 100)}{(\text{Total Cholesterol})}$			
Before treatment	28.7 ± 0.77	27.9 ± 0.26	28.0 ± 0.25
After treatment	28.7 ± 0.49	29.8 ± 0.27	29.6 ± 0.24

CONCLUSIONS

The rice diet causes a decrease in total, free and esterified serum cholesterol in patients with hypertensive vascular disease.

Of the 154 patients studied, 125 had a total serum cholesterol concentration greater than 220 mg. per 100 cc. before the rice diet was started. Twenty-nine patients had a serum cholesterol of 220 mg. per 100 cc. or less.

The total cholesterol and the esterified cholesterol decreased in 149 of the 154 patients. The free cholesterol decreased in 140 patients. There was no change in the mean ratio of free to total cholesterol in those patients whose initial total cholesterol was 220 mg. per 100 cc. of serum or less. There was an increase in the mean ratio of free to total cholesterol in those patients whose initial total cholesterol was 221 mg. per 100 cc. or more.

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Bilateral Thoracolumbar Sympathectomy for Hypertension*

A Study of 500 Cases

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DURING the period January, 1942, to July, 1948, 500 patients with hypertensive disease were operated upon by Dr. J. William Hinton† or members of the resident staff of the University Hospital, New York City. This report constitutes a review of this experience. Most of the operations were done at the University Hospital; a considerable number at the Doctors Hospital; and a few each at Bellevue Hospital and Women's Infirmary, New York City, and the Jersey City Medical Center, Jersey City, New Jersey.

METHOD OF STUDY

Records were kept by one of the surgeons for the entire group and a great majority of the patients were seen at his office or at the Sympathectomy Clinic of the University Hospital. Blood pressure readings were taken by one of three nurse-technicians associated with the study since its inception. In all cases an effort was made to secure observations at three, six, nine and twelve months after operation and at six-month intervals thereafter. Electrocardiograms, heart size (6 foot chest x-ray), routine urinalysis and blood urea nitrogen and nonprotein nitrogen determinations for comparison with preoperative data were recorded at the end of the first postoperative year and as often thereafter as indicated. A questionnaire was sent to unavailable, out-of-town patients and was filled in by the attending physician.

† It was Dr. Hinton's decision that analysis of the results of surgery would best be accomplished by a medical group since evaluation was primarily in the medical domain. He has, therefore, refrained from participation in any part of this review.

The number of patients and the duration of the period of observation (i.e., from time of operation to end of study, March 1, 1949) is indicated below. The mean observation period was 35.3 months. The longest period of observation was eighty-four months, the shortest six months.

Duration of Observation (yr.)	No. of Patients
0–0.9	34
1.0–1.9	85
2.0–2.9	155
3.0–3.9	126
4.0–4.9	72
5.0–5.9	10
6.0–6.9	18
Totals	500

PREOPERATIVE STATUS OF THE PATIENTS

In reviewing an experience of this kind it seems advisable to outline the preoperative findings in such manner that the observations may be compared with those in other operated and medically treated groups of hypertensives. The source of our data in the first 290 cases was the medical history and physical examination of the admitting surgical house officer, frequently supplemented by the records of the referring physician or the medical service of the University Hospital. In the last 210 cases this was supplemented by observations of either of two of the authors. (W. J. W.) and (J. J. T.). This variety in source material, particularly in the early cases, accounts for gaps in certain important items (e.g., ocular funduscopic examinations were not obtained in forty cases).

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Sex and Color. In this series females outnumber males by 298 to 202, a ratio of 3:2, and the group includes only 6 nonwhite patients. The predominance of females in our series is similar to that of medically treated groups reported by Rasmussen and Boe[1] M—31 per cent, F—69 per cent; Palmer et al.[2] M—45 per cent, F—55 per cent; and Perera's group[3] M—37 per cent, F—63 per cent; but differs from that of Keith, Wagener and Barker[4] M—65 per cent, F—35 per cent. The sex distribution in other series of operated hypertensives was similar to ours: Smithwick[5] M—39.4 per cent, F—60.6 per cent; Lemon and Poppen[6] M—42 per cent, F—58 per cent; Peet[7] M—48 per cent, F—52 per cent.

Age. The age distribution at the time of operation in periods of ten years is recorded in the following table:

TABLE I

Age	No. of Cases	% of All Cases
10–19	4	0.8
20–29	31	6.2
30–39	123	24.6
40–49	252	50.4
50–59	87	17.4
60 and over	3	0.6
Totals:	500	100.0

Half of the group were forty to forty-nine years of age; one-quarter were thirty to thirty-nine; slightly more than one-sixth were fifty to fifty-nine. The youngest patient operated upon was ten years old, the oldest sixty-three.

The age distribution of Rasmussen and Boe's series[1] showed more subjects in the older age groups; 34 per cent were fifty to fifty-nine; 41 per cent were sixty to sixty-nine; and 13 per cent were seventy to seventy-nine. Palmer's group[2] were also somewhat older. A detailed age distribution is not available in Keith, Wagener and Barker's[4] study but with respect to the maximum, minimum and mean ages their group was similar to ours. The age distribution of Perera's[3] group is recorded in terms of age at the time of the onset of the disease. The age distribution among the surgically treated patients reported by Peet[7] is practically identical with ours; in Smithwick's[5] series there are more patients aged thirty to thirty-nine and fewer in the fifty to fifty-nine year group; Lemon and Poppen[6] operated on the largest group of patients in the lower age brackets.

TABLE II

Years	No. of Cases	% of All Cases
Under 1	53	10.6
1–1.9	37	7.4
2–2.9	51	10.2
3–4.9	86	17.2
5–9.9	137	27.4
10–14.9	85	17.0
15 and over	51	10.2
Totals:	500	100.0

Duration of Known Hypertension. This information resolves itself into how well the patient remembers when he first learned of his elevated blood pressure. Although 40 per cent of the patients were specifically questioned as to the date of the last recorded normal blood pressure (insurance examinations, previous hospitalizations for nonhypertensive disorders, draft board examinations, etc.), the information is of dubious accuracy. However, similar data for other medically treated and sympathectomized groups suffer the same deficiency. As may be seen (Table II) slightly more than one-quarter of our group had known of their hypertension for from 5 to 9.9 years and nearly three-quarters of the group for three or more years.

Symptoms in Order of Frequency. With due regard for the fact that the symptoms complained of by hypertensive patients are not necessarily related to their underlying disease, these are listed herewith in descending order of frequency (Table III).

It is of interest that a stroke was recorded in the history of one-sixth of our cases, although many were minor in character and without clinical residua. Serious loss of vision was present in less than 4 per cent and

myocardial infarction in 2.4 per cent. No symptoms were present in 3.4 per cent, their major worry or the worry of their physicians was elevation of blood pressure alone.

Organ Involvement Indicated by Chief Complaint. Seventy per cent of our cases had symptoms referable to the head. (Table IV.) This is of interest because it is doubtful if this area represented in fact the actual source of danger to life since the great majority of any unselected group of hypertensives will die a cardiac death.[3]

TABLE III

Symptoms	No. of Cases	Incidence—%
Headaches:		
Mild 150	412	30.0
Severe 262		52.4 } 82.4
Dyspnea	297	59.4
Nervousness	191	38.2
Vertigo	189	37.8
Blurring of vision	171	34.2
Fatigue	168	33.6
Angina	142	28.4
Nocturia	128	25.6
Stroke	83	16.6
Paresthesias	82	16.4
Edema	77	15.4
Confusion (usually episodic)	22	4.4
Rapid change in vision	19	3.8
Orthopnea	18	3.6
Paroxysmal dyspnea	16	3.2
Myocardial infarction	12	2.4
Irritability	12	2.4
Unilateral blindness	6	1.2
No symptoms	17	3.4

Previous History of Glomerulonephritis. Seventeen patients (3.4 per cent) specifically stated that they had had nephritis previously, or described a renal illness associated with an antecedent streptococcal infection which could be labeled nephritis, or had a history of albuminuria antedating their hypertension. The number of these whose hypertension was causally related to the kidney disease is impossible to estimate; several who came to autopsy showed only renal arteriolar sclerosis and not the changes of glomerulonephritis. Others in this group did not show anemia, impairment of renal function or urinary findings suggestive of glomerulonephritis. Renal biopsies were made in 223 cases. Microscopic examination did not clarify the situation; only three had findings of glomerulonephritis and none of these had a clinical history of any type of renal disease; five of the biopsied cases had a clinical history of glomerulonephritis and none of these showed the pathologic changes of that disease.

TABLE IV

Major System to Which Chief Complaint Referred	No. of Cases	% of All Cases
Cerebral	350	70.0
Cardiac	78	15.6
Eyes	28	5.6
General	27	5.4
Blood pressure alone	17	3.4
Totals	500	100.0

Previous History of Pyelonephritis. There were sixteen cases (3.2 per cent) with a history of pyelonephritis. All were biopsied but only one showed pathologic changes compatible with this disease. In the first 200 cases routine intravenous pyelography was performed but the small amount of helpful information obtained, and one death due to iodide sensitivity, prompted abandonment of this as a routine procedure. In the succeeding cases intravenous or retrograde pyelography was carried out when the clinical history or laboratory findings indicated its advisability.

Previous History of Toxemia of Pregnancy. Almost one-quarter (seventy) of the females in the series gave a history of toxemia of pregnancy. Repeated episodes are counted only once. The relationship of the onset of hypertensive disease to toxemia has not been analyzed in this study.

Physical Findings in Order of Frequency. Forty cases or 8.0 per cent of the series do not include a record of the preoperative eyeground findings. Heart size was not included in this tabulation. This has been analyzed from six-foot chest films.

Basal systolic murmurs were considered worthy of tabulation as an index of either

aortic dilatation or atherosclerosis. Enlargement of the liver is included because in some instances it was probably cardiac in origin.

TABLE V

Physical Findings	No. of Cases	Incidence—%
Ocular fundi with positive findings:		
Grade II	151	30.2
Grade I	87	17.4
Grade III	79 (371)	15.8 (74.2)
Grade IV	54	10.8
Basal systolic murmur	81	16.2
Enlarged liver	32	6.4
Residue of hemiplegia	25	5.0
Pulmonary rales	17	3.4
Confusion	13	2.6
Edema	10	2.0
Pulsus alternans	6	1.2

Predominant Physical Findings Indicating Major Organ Involvement. It was deemed also of interest to tabulate the predominant organ involvement as determined by physical examination alone:

TABLE VI

Findings	No. of Cases	% of All Cases
Blood pressure alone	348	69.6
Eyes	124	24.8
Cerebral	23	4.6
Cardiac	5	1.0

An elevated blood pressure alone was the outstanding physical disorder in 69.6 per cent of cases. Eyeground changes ranked second; predominance of cerebral and cardiac abnormalities was found by physical examination *alone* in a relatively small fraction of the group.

Distribution of Cases According to Diastolic Blood Pressure. Evaluation of blood pressure determinations is widely recognized as difficult. It is well known that the systolic blood pressure may vary greatly in a given individual and does not usually reflect increased peripheral resistance. In comparing pre- and postoperative determinations, if one considers both the systolic and diastolic pressures or a combination of pulse pressure and diastolic pressure, the range of variability, not to say confusion, increases to a formidable degree. For this reason we have compared only diastolic blood pressure readings in our preoperative evaluation and postoperative studies. We have classified our patients into groups separated by 20 mm. Hg to allow for day to day variation and for the variation among observations by several individuals on the same patient. Those values designated as "Admission Lying Diastolic Blood Pressure" were those obtained within a few hours of admission to the hospital by a house physician. These probably correspond to readings obtained by the referring physician in his office. After the patient had been hospitalized two or more days and was on a modified rest regimen, a trained nurse technician recorded the Lying Blood Pressure preliminary to a sodium amytal test.[8] We believe that this approaches a baseline value and reflects a lessening or abolition of the effects of recent physical effort (i.e., coming to the doctor's office or hospital) and superficial psychic stimuli (the effects of a new environment, a strange physician, etc.). Subsequent to this the Sitting, Standing and Standard Exercise pressures were obtained. The Standard Exercise consisted in having the subject step up and down on a platform one foot high, twenty times, raising his arms over his head with each step. Only the Exercise blood pressure has been tabulated since Sitting and Standing blood pressures usually ranged between Lying and Exercise values. We have assumed that Exercise blood pressure level approximates levels attained during moderate exercise and perhaps emotional stress in the patients' everyday life. Table VII on page 504 notes the range of diastolic blood pressures obtained under these several conditions.

Not unexpectedly among the Lying Diastolic readings, 38 per cent are under 120 mm. Hg and slightly more than 5 per cent are under 100 mm. Hg. Sixty-two per cent of the cases had a Resting Diastolic blood pressure in excess of 120 mm. Hg. Admission and Exercise diastolic blood pres-

sures show a significant shift to the higher ranges, although the difference between Admission and Exercise levels was not significant. Under these conditions about 80 per cent of the cases had a Diastolic blood pressure over 120 mm. Hg, and about 40 per cent were 140 mm. Hg or over.

TABLE VII
PREOPERATIVE DIASTOLIC BLOOD PRESSURE

Blood Pressure in mm. Hg	Admission		Lying		Exercise	
	No. of Cases	% of All Cases	No. of Cases	% of All Cases	No. of Cases	% of All Cases
160 and over	53	10.6	20	4.0	49	9.8
140–159	137	27.4	83	16.6	167	33.4
120–139	206	41.2	207	41.4	205	41.0
100–119	100	20.0	164	32.8	74	14.8
Under 100	4	0.8	26	5.2	5	1.0
Totals:	500	100.0	500	100.0	500	100.0

Laboratory Data. Four simple laboratory tests have proved to be of practical use in the evaluation of the hypertensive state and all are available in most general hospitals. They are the specific gravity of the urine (in a majority of cases this was checked by means of a suitable concentration test), blood urea nitrogen, electrocardiogram and six-foot roentgenogram of the chest for heart size.

TABLE VIII
PREOPERATIVE SPECIFIC GRAVITY OF URINE

Specific Gravity	No. of Cases	% of All Cases
1.020 or over	253	50.6
1.011–1.019	208	41.6
1.010 or under	27	5.4
Unknown	12	2.4
Totals:	500	100.0

Moderate impairment of concentrating power was seen in 41.6 per cent of cases; marked impairment in 5.4 per cent. About three-quarters of the cases had blood urea nitrogen levels of 15 mg. per cent or less; only 5.6 per cent exceeded 21 mg. per cent. A normal electrocardiogram was reported in 35.2 per cent; moderate changes were reported in 42.8 per cent; marked in 17.8 per cent. Previous myocardial infarction was seen in 2.2 per cent either as an independent finding or in combination with ventricular hypertrophy. No electrocardiogram was available in 2.8 per cent. Slightly more than half the cases showed cardiac enlargement and almost one-fourth showed dilatation of the aorta.

TABLE IX
PREOPERATIVE BLOOD UREA NITROGEN

Blood Urea Nitrogen (mg. %)	No. of Cases	% of All Cases
15 or under	380	76.0
16–20	65	13.0
21–30	17	3.4
Over 30	12	2.4
Unknown	26	5.2
Totals:	500	100.0

TABLE X
PREOPERATIVE ELECTROCARDIOGRAM

Interpretation	No. of Cases	Incidence—%
Normal	176	35.2
Mild left ventricular hypertrophy	214	42.8
Marked left ventricular hypertrophy	89	17.8
Previous myocardial infarction	11	2.2
Unknown	14	2.8

TABLE XI
PREOPERATIVE SIX-FOOT CHEST X-RAY

Interpretation of Heart Size	No. of Cases	Incidence—%
Normal	187	37.4
Enlarged	281	56.2
Dilated aorta	110	22.0
Unknown	32	6.4

Sodium amytal tests were carried out on our cases but they are not analyzed in this

report. Our experience has borne out the findings of a preliminary study by Hinton and Lord[8] that this test does not correlate well with the results to be expected from sympathectomy.

Distribution of Cases by Palmer's Modification of the Keith-Wagener-Barker Classification. While the preceding material provides a fairly adequate over-all impression of the patients operated upon, a more precise classification is desirable. The grading of hypertensives according to the method of Keith, Wagener and Barker[4] has been utilized at this hospital, although the frequent disparity between the vascular changes seen in the fundi and those present in other organs here, as elsewhere, has limited its usefulness. This was recognized by Palmer, Loofbourow and Doering[2] in their study of 430 patients with hypertension treated medically for an average of eight years. They have formulated a four-part classification similar to that of Keith, Wagener and Barker[4] which considers damage to other organs in addition to eye-ground changes. We have applied their criteria to our cases. In the forty cases in which no funduscopic data were available there was evidence of other organ involvement sufficient to categorize them in grade II or III in twenty-two cases. In the remaining eighteen, although the other organ systems were negative, they are called Unclassified rather than Grade I. The criteria of Palmer et al.[2] are as follows:

"Grade I:—These patients have no changes or minimal changes in the fundi as represented by narrowing of the arterioles, normal hearts or no more than prominence in the region of the left ventricle by x-ray study, no impairment of renal function by the tests used and normal urine examination or occasionally slight albuminuria and slight changes on microscopical examination of the sediment.

"Grade II:—These cases include moderate organic changes in the fundi: widening of the arteriolar light reflex, narrowing, caliber changes and arteriovenous compression. The heart exceptionally is normal by x-ray study and is usually prominent in the region of the left ventricle and sometimes more definitely enlarged but without functional impairment; the kidney is normal, slight degrees of albumin and minimal numbers of formed elements are found in the sediment, or there may be slightly impaired function.

TABLE XII

University Hospital Series			Medically Treated Series (Palmer)		
Grade	No. of Cases	% of All Cases	Grade	No. of Cases	% of All Cases
I	96	19.2	I	104	24.2
II	81	16.2	II	80	18.6
III	251	50.2	III	192	44.8
IV	54	10.8	IV	54	12.4
Unclassified	18	3.6	...	...	.....
Totals:	500	100.0		430	100.0

"Grade III:—These fundi are rarely normal, usually showing arteriolar narrowing, caliber changes, wide light reflex and arteriovenous compression. Often, there are exudates and hemorrhages; the heart is often moderately to markedly enlarged, commonly with symptoms and signs of actual or impending congestive failure or symptoms of anginal failure. The urine frequently shows albuminuria and casts, and renal function is often impaired, though actual failure (uremia) is not common; cerebral accidents sometimes occur (in 20 per cent of cases).

"Grade IV:—The cardinal, indeed, the obligatory signs is edema of the optic discs, with or without exudates and hemorrhages and always with marked narrowing of the arterioles. Cardiac enlargement and congestive failure may be present; renal impairment and failure are common."

Using these criteria a tabulation of the relative severity of the hypertensive process in our patients was compared with Palmer's group of medically treated patients. The close approximation of the several grades of

severity in our patients with those medically treated is apparent. (Table XII.)

OPERATIVE PERIOD

This phase of the study concerns the events occurring from the time of the first operation through the day on which the patient left the hospital.

Types of Operative Procedure. In our initial experience with this operation the sympathetic chain from lumbar-3 or -2 through thoracic-8 was removed, the original Smithwick[5] procedure. As follow-up studies in the first year or two of this experience indicated either a failure of sustained lowering of the blood pressure or a rise in blood pressure to preoperative levels in a number of cases, it was hoped that more extensive ganglionectomy might give more marked and/or more lasting results. This possibility, together with improvement in operative technic and immediate postoperative care, led to the extension upward of the levels at which ganglia were removed. In attempting to evaluate this procedure and to weigh the potential disadvantage of increased operative mortality and morbidity the cases are grouped according to the level of ganglion resection. Inasmuch as the two sides were not always done to the same level the classification was based on the highest level resected on either side. The levels chosen and the number of cases in each group are shown herewith:

TABLE XIII
TYPES OF OPERATION BY MAXIMUM LEVEL OF GANGLION RESECTION

Operative Level	No. of Cases	% of All Cases
T-8 or lower	182	36.4
T-7 to T-4 inclusive	147	29.4
T-3 and T-2	134	26.8
T-1	37	7.4
Totals:	500	100.0

Slightly more than one third of the cases had the least radical form of surgery. Operations of moderate extent were done in more than one-half of the cases and only 7.4 per cent had the most radical procedure approaching a total sympathectomy.

Immediate Postoperative Complications. The immediate postoperative outlook of the patient, granting a high order of surgical technique and skillfully administered anesthesia, is influenced primarily by postoperative complications:

TABLE XIV

Complication	No. of Cases	Incidence—%
Hemothorax	196	39.2
Temporary elevation of blood urea N above 25 mg. %	74	14.8
Cerebral accident	31	6.2
Pneumonia	26	5.2
Atelectasis	18	3.6
Cardiac failure	18	3.6
Other (shock, empyema, wound infections, etc.)	17	3.4
Myocardial infarction	8	1.6
Pulmonary embolism	4	0.8

Some of these events are to be anticipated in any major surgical procedure, e.g., pulmonary embolism, shock, wound infection, etc. Certain other difficulties stem quite naturally from the operative area involved, e.g., hemothorax, pneumonia and atelectasis. Others such as temporary elevation of the blood urea nitrogen, cerebral vascular accident and myocardial infarction reflect the fact that these patients have underlying vascular disease of the kidney, brain or heart. With respect to hemothorax and temporary nitrogen retention, we have come to think of them as "postoperative sequelae," rather than "postoperative complications."

Table xv details the complications according to the operative levels.

The incidence of hemothorax appears to be directly related to the extent of the operative procedure. This might be expected since the higher the level of ganglionectomy the more tissue is exposed from which blood may escape and the greater becomes the technical problem of hemostasis. The incidence of cardiac failure, in a small number of cases resected above the

level of T-8, also appears to increase except in the T-2–T-3 group. The remainder of the complications do not show a proportionate rise with each operative level, merely a significant rise in incidence at any level above the original levels recommended by Smithwick.[5]

The mortality in patients under age thirty is significantly lower than that of the older groups. Though there is a slight rise in the mortality from thirty to sixty years of age this difference is not statistically significant. Individuals over fifty in our experience do not run a greater risk than do those between

TABLE XV

OCCURRENCE OF IMMEDIATE POSTOPERATIVE COMPLICATIONS FOLLOWING VARIOUS LEVELS OF GANGLION RESECTION

Complications	T-8 or Lower		T-7 to T-4		T-2 to T-3		T-1	
	No. of Cases	Incidence %	No. of Cases	Incidence %	No. of Cases	Incidence %	No. of Cases	Incidence %
Hemothorax	10	5.5	56	38.1	95	70.9	35	94.7
Temporary elevation of blood urea above 25 mg. %	12	6.6	30	20.4	23	17.2	9	24.3
Cerebral accident	7	3.8	8	5.4	13	9.7	3	8.1
Pneumonia	10	5.5	6	4.1	7	5.2	3	8.1
Atelectasis	2	1.1	7	4.8	7	5.2	2	5.4
Cardiac failure	5	2.7	7	4.8	2	1.5	4	10.8
Myocardial infarction	1	0.6	4	2.7	3	2.2	0	0
Pulmonary embolism	0	0	1	0.7	2	1.5	1	2.7
Intercostal neuralgia	30	16.5	73	49.6	70	52.3	17	46.0

Immediate Postoperative Morbidity and Mortality. This was taken to be the length of time the patient remained in the hospital after the first side was operated upon. In general, the stay in the hospital was five to ten days longer following operations above T-8.

Any patient who died between the day of the first operation and day of discharge was considered to be an operative death. A total of forty-four patients were in this category, an over-all mortality rate of 8.8 per cent.

There was no significant difference in the operative mortality between males and females:

TABLE XVI

	No. of Deaths	No. of Cases	Mortality —%
Males	20	202	9.9
Females	24	298	8.1

the ages thirty to thirty-nine and forty to forty-nine. (Table XVII.)

TABLE XVII

Age in Years	No. of Deaths	Mortality—%
10–19	0	0
20–29	1	3.2
30–39	10	8.1
40–49	24	9.5
50–59	9	10.3
60 and over	0	0

Table XVIII lists the distribution of deaths by general causes.

Cerebral and cardiac deaths were approximately equal in number, each constituting the mode of death in about one-third of those who succumbed. Renal failure was a primary cause of death in 6.8 per cent of cases. This relatively low figure may be due to the fact that since the first hundred cases demonstrated that a slightly elevated blood urea is a warning signal of partial or

complete postoperative renal failure, these cases have been more rigorously excluded from consideration of sympathectomy than any others. On the other hand, patients who died cardiac or cerebral deaths often had minimal or no premonitory signs or, if present, these were not acknowledged clinically as significant. Two patients with pheochromocytoma died. One had been tentatively diagnosed preoperatively but an exhaustive work-up failed to confirm its presence. (Recent diagnostic aids were not available at that time.) The other was unsuspected.

TABLE XVIII

Cause	No. of Deaths	% of All Deaths
Cerebral	16	36.3
Cardiac	15	34.0
Renal	3	6.8
Pheochromocytoma	2	4.5
Other (shock, retroperitoneal hemorrhage, mediastinitis, etc.)	8	18.4
Totals	44	100.0

Operative Deaths in the Various Types of Operation. There is a significant rise in the death rate when ganglia above T-8 are removed:

TABLE XIX

Types of Operation	No. of Deaths	Mortality—%
T-8 or lower	7	3.8
T-7 to T-4	15	10.2
T-2 to T-3	14	10.4
T-1	8	21.6

There is no significant difference in the mortality incurred by extending the operation from T-4—T-7 up to T-2 or 3. The apparent additional rise in mortality when the operation includes T-1 is not statistically significant due to the smaller number of cases in this group.

RESULTS

The analysis of the results of any form of therapy for hypertension is a complicated problem. Objections can be raised to almost all criteria of improvement. Blood pressure alone does not necessarily measure the hypertensive state; subjective evaluation always includes the effects of the postoperative course versus the severity of the preoperative symptoms; laboratory data often contradict both blood pressure results and subjective impressions; arbitrary classification is befogged by a cloud of definitions.

We have analyzed our results using all of the customary criteria but are not reporting them here; rather, we have chosen to detail conclusions concerning some of this data.* With this type of information, summary is difficult and generalization dangerous. However, considering only the blood pressure, it would appear that at the end of a five-year follow-up:

Those cases with a preoperative resting "controlled" diastolic blood pressure 160 mm. Hg or higher had a high death rate (50 per cent) but about half the survivors showed a drop of at least 20 mm. Hg in their diastolic blood pressure.

Those cases with a preoperative resting "controlled" diastolic blood pressure of 140–159 mm. Hg had a death rate of 35 per cent. The survivors showed a drop of at least 20 mm. in the diastolic blood pressure in 50 to 60 per cent of cases.

Those cases with a preoperative resting "controlled" diastolic blood pressure between 120–139 mm. Hg had a death rate of 22.2 per cent. The survivors showed a drop of at least 20 mm. in the diastolic blood pressure in 40 to 60 per cent of cases.

Those cases with a preoperative resting "controlled" diastolic blood pressure of 100–119 mm. Hg had a death rate of 13.4 per cent. The survivors showed a postoperative diastolic blood pressure under 100 in about 25 per cent of cases.

Those cases with a preoperative resting "controlled" diastolic blood pressure under 100 mm. Hg had a death rate of 11.5 per

* The data for this section have been calculated and are available in tabular form to those who are interested. For editorial reasons they have been eliminated from this presentation.

cent. The survivors showed diastolic blood pressure levels under 100 mm. in about 50 per cent of cases.

Stated another way, those cases with a preoperative resting diastolic blood pressure over 120 mm. Hg showed an appreciable sustained drop in blood pressure in about half the cases. Those with a preoperative blood pressure under 120 mm. Hg showed a less dramatic change. The over-all death rate of those followed for five years was roughly proportional to the height of the blood pressure.

Postoperative Exercise Diastolic Blood Pressure Levels. The high percentage of low postoperative exercise blood pressure supports the clinical observation that one of the outstanding results of sympathectomy is a reduction in blood pressure following exercise as compared with the customary rise in blood pressure seen in normals and hypertensives following exercise. Similar though less marked changes are seen on changing from the supine to the standing position.

It is recognized that in the early postoperative months this postural hypotension is an unpleasant side effect of sympathectomy, often requiring the use of elastic stockings and abdominal binders. Ultimately, however, we believe that this may be the most salutary result of sympathectomy, reducing the level of diastolic blood pressure during that part of the day when the patient is most active. Theoretically this should reduce the work load on the heart and should protect the cerebral vascular tree from peaks of elevation coincident with effort. It has not been determined whether or not a similar protective effect is available against elevation due to psychic stimuli.

Effect on Blood Pressure of Various Levels of Ganglion Resection. Since the more radical forms of surgery have been done only during the last two years of the study, long-term comparisons could not be made. Comparison of results at the end of the first postoperative year revealed no significant difference among these groups.

Subjective Evaluation. Improvement was noted during the first year by 80 per cent of the patients. This feeling of satisfaction gradually tapered off so that during the fourth year of follow-up only 59.0 per cent viewed their results as improvement over their preoperative state. After five or more years postoperatively only 53.4 per cent felt improved; however, it should be noted that the unknowns in this category were some 26.6 per cent of the total compared to an unknown rate of 2.3 per cent to 13.6 per cent for the first four years. The number of individuals who were "worse" or "uncertain" during the entire period was fairly constant throughout: 2.1 per cent to 5.0 per cent for the former, and 4.3 per cent to 8.3 per cent for the latter. "No change" paralleled "uncertain" for the first three years but rose to the vicinity of 20 per cent in the fourth and fifth year periods. The statistical significance of this is doubtful in view of the numbers involved.

The decline in the percentage of subjective improvement has several explanations. One is the return of symptoms due to hypertension in some of the cases with a poor postoperative result; second is persistent side effects of sympathectomy (e.g., intercostal neuralgia) growing in importance in the patient's mind as his recollection of his preoperative complaints becomes less vivid with the passage of time. Third is the persistence or recurrence of symptoms originally ascribed to hypertension but actually not due to it (e.g., migraine headaches, nervousness, etc.).

In spite of this decline in the subjective feeling of improvement over a period of years we believe this information is of interest to both the patient and the doctor indicating, as it does, a rate of improvement of 50 to 60 per cent after five years. If all subjective improvement in sympathectomized hypertensive subjects be considered as psychologic in origin, one must grant that it is a profound psychic effect which is still manifest five years after treatment.

Effects of Operation on the Ocular Fundus. In patients with normal fundi or those showing minimal (grade 1) alterations the changes following operation were not re-

markable; thirty cases (38.5 per cent) and seventeen cases (22.7 per cent), respectively, were graded as worse. In most instances this represented a change from normal to grade I to II; a result in many cases of a difference in interpretation by different observers. In fundi with more serious changes the degree of beneficial change became more striking: twenty-five cases (20.1 per cent) of grade II, twenty-three cases (39.0 per cent) of grade III and sixteen cases (66.7 per cent) of grade IV showed improvement. The most spectacular and usually the most important functional changes were seen in those with grade IV fundi, in whom papilledema, hemorrhages and exudates disappeared and vision returned to normal.

Postoperative Electrocardiograms. Electrocardiograms were obtained in 33.7 per cent of those survivors who had had preoperative electrocardiograms. Most of the tracings were made more than a year after operation. The patients with normal preoperative electrocardiograms showed a low incidence of change. Eight (5.3 per cent) were worse, seven developed left ventricular hypertrophy, one suffered a myocardial infarction and forty-nine (30.8 per cent) showed no change. Of those with mild left ventricular hypertrophy twenty-three cases (13.2 per cent) showed improvement and twenty-seven (15.4 per cent) no change. Only one record was interpreted as worse. Moderate to marked left ventricular hypertrophy showed improvement in five cases (10.9 per cent), no change in eleven (23.9 per cent) and an increase in abnormal changes in five cases (10.9 per cent). Cases with a myocardial infarction preoperatively or without a preoperative electrocardiogram had such a poor follow-up that comment is valueless.

Postoperative Heart Size. Chest x-rays for heart size were obtained in 28.7 per cent of the survivors who had been x-rayed preoperatively. Patients with normal heart size showed no change in thirty-seven (25.1 per cent). Enlargement appeared for the first time after operation in five cases (3.4 per cent). Diminution of heart size was noted in twenty-seven (12.3 per cent) of those with preoperative enlargement, no change occurred in thirty-five cases (15.9 per cent) and further enlargement was apparent in two cases (0.9 per cent).

Postoperative Blood Urea Nitrogen Levels. These determinations were available in 30.4 per cent of the survivors. Of the patients with a preoperative blood urea level of 15 mg. per cent or under, fifty-four cases (17.2 per cent) showed no change. Thirty-six cases (11.4 per cent) are tabulated as worse, though in most cases this represented only a slight rise in blood urea level (e.g., from 15 mg. per cent to 16–20 mg. per cent). Of the forty-six survivors with borderline blood levels of 16–20 mg. per cent, seven (15.2 per cent) dropped down to normal levels; five (10.9 per cent) showed no change and six (13.0 per cent) moved into definitely elevated levels of 20 mg. per cent or more. Of the six survivors with an initial blood urea between 20–30 mg. per cent two showed an elevation in their postoperative blood levels and four were unknown. Of the five survivors with preoperative blood urea levels above 30 mg. per cent two showed a lowering of the postoperative urea level to below 30 mg. per cent, one showed no change and two were unknown.

Postoperative Results Tabulated According to Arbitrary Classification. Thus far we have confined our study to selective results on various signs and symptoms of the hypertensive process following sympathectomy. It seemed advisable to apply a more generally accessible evaluation of our experience, somewhat more rigid but less confusing. In the final analysis, one wishes to know how frequently a satisfactory blood pressure and subjective result was obtained. To answer this question we have classified our results as follows:

Excellent: Subjective improvement together with a standing* diastolic blood pressure under 100 mm. Hg, the original standing diastolic blood pressure having been over 125 mm. Hg.

* Standing blood pressure values were used because they represent mid-points between the low values after exercise and the higher values obtained at rest.

Good: Subjective improvement together with a significant drop (25 mm. Hg or more) in standing diastolic blood pressure the level remaining at or above 100 mm; or, subjective improvement together with a significant drop (25 mm. or more) in standing diastolic blood pressure, the original standing diastolic blood pressure being less than 125 mm. Hg.

TABLE XX
OVER-ALL RESULTS—ALL CASES

Results	No. of Cases	% of All Cases
Excellent	49	9.8
Good	86	17.2
Fair	146	29.2
Poor	59	11.8
Dead—Operative	44	8.8
After operative period and due to high blood pressure	53	10.6
After operative period and due to other causes	14	2.8
Unknown	49	9.8
Totals	500	100.0

Dead: Died as a result of their disease; (1) operative deaths, (2) outside the operative period and (3) died of other causes.

Unknown: Those patients operated upon over one year before the conclusion of this follow-up study (March, 1949) on whom no follow-up data had been obtained during the year immediately preceding the above date.

As indicated in Table xx, excellent results were obtained in 9.8 per cent; good results in 17.2 per cent; fair results in 29.2 per cent; poor results in 11.8 per cent; 22.2 per cent of the patients were dead at the time of follow-up, 8.8 per cent in the course of the operation period; 10.6 per cent as a result of their disease beyond the immediate operative period, and 2.8 per cent of causes unrelated to hypertension or to the operation after the operative period; 9.8 per cent were classified as unknown although we know that at least half of these were alive at the time these data were collected.

Over-all Results in Relation to the Severity of the Preoperative Hypertension. Table xxi details the results in accordance with the several grades of the disease as classified by Palmer's modification of the method of Keith, Wagener and Barker.

TABLE XXI
FINAL RESULTS ACCORDING TO THE SEVERITY OF THE PREOPERATIVE HYPERTENSION

Results	I	%	II	%	III	%	IV	%	Unclassified	%
Excellent	10	10.4	15	18.5	18	7.2	3	5.6	3	16.6
Good	19	19.8	21	25.9	37	14.7	5	9.3	4	22.2
Fair	36	37.6	26	32.0	68	27.0	9	16.7	7	38.9
Poor	13	13.5	5	6.2	34	13.5	5	9.3	2	11.1
Death—Total	8	8.3	9	11.2	63	25.3	30	55.4	1	5.6
Operative	2 ..	.....	2 ..	.....	30 ...	.....	10 ..	.....	0 ..	.....
Postoperative due to high blood pressure	3 ..	.....	5 ..	.....	26 ...	.....	18 ..	.....	1 ..	.....
Other	3 ..	.....	2 ..	.....	7 ...	.....	2 ..	.....	0 ..	.....
Unknown	10	10.4	5	6.2	31	12.3	2	3.7	1	5.6
Totals	96	100.0	81	100.0	251	100.0	54	100.0	18	100.0

Fair: A poor to indifferent subjective response with a significant drop (25 mm. or more) in standing diastolic blood pressure; or, subjective improvement without a significant drop in standing diastolic blood pressure (a drop of less than 25 mm.).

Poor: The remainder of the living.

Inspection of the excellent results suggests that group II had a higher rate of improvement than any other group classification save the unclassified. However, this differ-

ence is only statistically significant with respect to groups III and IV. The difference between groups I and II is not statistically significant nor is group I significantly higher than groups III and IV. Similar findings hold for the good results. The superiority of group II only holds true with regard to groups III and IV statistically. There is no statistical difference between groups I and II. Fair results were quite uniform for groups I, II and III but group IV was significantly lower than groups I and II.

Total deaths show no statistical significance between groups I and II but there is a progressive rise in the rate of about 10 per cent for groups I and II to 25.3 per cent for group III and 55.4 per cent for group IV. These differences are clearly significant. Operative deaths are not appreciably different in groups I and II but there is a significant rise between these and the number of deaths in groups III and IV. There is no statistically significant difference between groups III and IV. Deaths after the operative period, due to hypertensive disease, were not significantly different between groups I and II or II and III but the difference between groups I and III or III and IV showed a significant rise with the more advanced classification.

The survival rate for the various groups for the period 35.3 months (mean duration between operation and the closing date of the follow-up study March, 1949) is as follows:

TABLE XXII A

Severity of Hypertension	Surgically Treated	Medically Treated (Palmer)
Group I	91.7	97
Group II	88.8	90
Group III	74.7	75
Group IV	44.6	16

Comparison of the figures in column 1 above with figures in column 2 (interpolated from the study by Palmer et al. of 430 cases of medically treated hypertensives) shows unequivocally that the survival rate in groups I, II and III is not significantly different whether the patients are treated surgically or medically. Only in group IV is there a significant difference in favor of the operated group.

It is of interest to show in detail the duration of observation of the patients in group IV:

TABLE XXII B

Duration of Observation (yr.)	Group IV Patients
0–0.9	4
1.0–1.9	10
2.0–2.9	7
3.0–3.9	16
4.0–4.9	7
5.0–5.9	4
6.0–6.9	6
Totals	54

The survival curves in Palmer's series at the four-year period are based on a follow-up of only 50 per cent, and at the eight-year mark they were able to study only 66.5 per cent of the original group of 646 patients. In contrast we have succeeded in documenting the course of 90.2 per cent of our group. It is possible although by no means certain that the survival curve of the medically treated group is actually poorer than it appears. Comparison with Keith, Wagener and Barker's original series[4] was not made because of the marked difference in the sex distribution between their series and ours. A similar comparison was recently made by Hammarström and Bechgaard.[9]

TABLE XXIII
CAUSES OF ALL DEATHS IN ALL CASES OF THE SERIES

Causes	No. of Deaths	% of All Deaths
Cerebral	32	28.9
Cardiac	36	32.4
Renal	14	12.6
Suicide	3	2.7
Pheochromocytoma	2	1.8
Other (not related to high blood pressure)	11	9.9
Unknown cause	13	11.7
Totals	111	100.0

Cardiac deaths lead (32.4 per cent); cerebral deaths are a close second (28.9 per

cent); renal deaths account for 12.6 per cent of the fatalities; suicide, pheochromocytoma, other deaths not related to high blood pressure, and deaths due to unknown causes constitute the remainder. We have not correlated the operative or total deaths with all the single items of preoperative data nor with any particular combinations of preoperative factors. However, certain theoretic considerations plus clinical observation, both on our part and by others, indicated that selective inquiry might be profitable.

TABLE XXIV

Results	No. of Cases	%
Operative deaths	10	12.1
Postoperative deaths	17	20.5
Survivors	56	67.4
Total number of cases	83*	100.0

* Twenty-five showed clinical residua; the mortality figures calculated separately were not significantly different from the group as a whole.

Mortality in Cases with a Preoperative History of a Cerebral-vascular Accident. Table XXIV relates a pre-existing cerebral vascular accident to operative and postoperative outcome. The operative mortality in this group is slightly higher than that for the entire series.

Mortality in Cases with a Preoperative History of Mental Confusion. It is apparent from data in Table XXV that mental confusion has a much more ominous significance:

TABLE XXV

Results	No. of Cases	%
Operative deaths	9	40.9
Postoperative deaths	7	31.8
Survivors	6	27.3
Total number of cases	22	100.0

The increase in the operative and postoperative mortality in the presence of mental confusion compared with that of the entire group is enough to make the risk of operation unwarranted.

Too few patients with immediate preoperative cardiac failure were operated upon to warrant statistical study.

TABLE XXVI

Results	No. of Cases	%
Operative deaths	17	11.9
Postoperative deaths	14	9.9
Survivors	111	78.2
Total number of cases	142	100.0

Mortality in Cases with a Preoperative History of Angina Pectoris. A history of angina pectoris (with due consideration paid to the validity of the symptoms) does not alter the mortality during or immediately after operation or in the remote postoperative period. (Table XXVI.)

Mortality in Cases with a Preoperative History of Myocardial Infarction. Patients with a history of myocardial infarction have an apparently higher mortality but the group is small. (Table XXVII.)

TABLE XXVII

Results	No. of Cases	%
Operative deaths	2	16.7
Postoperative deaths	2	16.7
Survivors	8	66.6
Total number of cases	12	100.0

Relationship of Mortality to the Level of Nitrogen Retention. A rise in the total death rate may be closely correlated with elevated preoperative blood urea nitrogen levels. As the levels rise the deaths increase. (Table XXVIII.)

Uremia was the cause of death in a significantly higher percentage of cases only when the urea nitrogen exceeded 20 mg. %. Sixty-one or 30.2 per cent of the males and fifty or 16.8 per cent of the females died in the operative and follow-up period. This is

in accord with the repeatedly observed fact that the outlook for male hypertensives is significantly poorer than that for females.

*Incidence of Hypertensive Complications Occurring after the Operative Period.** In addition to alleviating symptoms and possibly prolonging life expectancy, one of the major motives for recommending sympathectomy has been the hope that certain complications occurring in the natural history of the disease might be averted. To study whether or not this objective was attained we tabulated the occurrence of various complications ascribable to hypertension or to its ally, atherosclerosis.

TABLE XXVIII

Blood Urea Nitrogen (mg. %)	Total No. of Cases	Operative Deaths		Postoperative Deaths		Survivors	
		No. of Cases	Mortality %	No. of Cases	Mortality %	No. of Cases	%
15 or less	380	29	7.8	37	9.7	314	82.5
16–20	65	9	13.8	10	15.4	46	70.8
21–30	17	5	29.4	6	35.3	6	35.3
Over 30	12	1	8.4	6	50.0	5	41.6
Unknown	26	0	0	8	30.8	18	69.2
	500	44		67		389	

TABLE XXIX

Complication	No. of Cases	Incidence in % among 456
Angina pectoris	39	8.5
Cerebral accident	38	8.0
Cardiac failure	17	3.7
Myocardial infarction	17	3.7
Uremia	12	2.6
Blindness	8	1.7
None	370	81.2
Unknown	22	4.8

One hundred thirty-one complications occurred in sixty-four people, fifty-three of whom died. A few of the conditions were present in some cases before operation or in the immediate postoperative period, i.e., angina pectoris and uremia, but most represent problems that arose for the first time after the individuals left the hospital. We know of no method whereby these observations may be compared with control groups since most other studies with such data have either been followed to death or for very long periods. It is therefore difficult to say whether the occurrence of these events is more or less frequent than in an unoperated group in this short space of time. Angina pectoris and cerebral accident head the list of complications each occurring in about 8.5 per cent of the survivors of the operation; myocardial infarction and cardiac failure each occurred in 3.7 per cent of the cases.

* Includes the dead for whom the cause of death was known.

CONCLUSIONS

1. Five hundred cases of hypertensive disease subjected to bilateral thoracolumbar sympathectomy between January, 1942, and July, 1948, are reviewed in detail.

2. Excellent results were obtained in 9.8 per cent; good in 17.2 per cent; fair in 29.2 per cent; poor in 11.8 per cent; unknown in 9.8 per cent; 22.2 per cent were known to be dead at the time of follow-up; 8.8 per cent as a result of hypertensive disease beyond the operative period and 2.8 per cent due to causes unrelated to hypertension.

3. Comparison of the survival curves of this group with a comparable medically treated group at the end of an average period of three years shows no statistically significant difference in groups I, II and III. In group IV, however, a significantly higher survival rate is apparent in the operated group.

4. In our experience the following should be considered as absolute contraindications to thoracolumbar sympathectomy: (1) Intractable cardiac failure; (2) renal insufficiency which presents a preoperative blood urea nitrogen level in excess of 20 mg. per cent; (3) evidence of mental confusion; (4) a history of a cerebral vascular accident or myocardial infarction less than six months before operation; (5) a history of a serious psychiatric disturbance at any previous period, e.g., manic-depressive psychosis, severe psychoneurosis, etc.

5. This study verifies the experience of others that a definite decrease in the diastolic blood pressure may be obtained in a significant number of patients over a fairly prolonged period, together with a reversal or amelioration in some patients of other manifestations of the hypertensive process, i.e., fundus changes, ECG, heart size, etc. The survival rate for hypertensive patients graded I, II and III by Palmer's modification of Keith, Wagener and Barker's classification has not been altered in this series and therefore the ultimate criterion for reversal of the hypertensive process has not been satisfied.

6. Whatever indications or contraindications for sympathectomy are held, it appears from our data that the operation of choice is the original Smithwick procedure. The degree of blood pressure reduction and subjective improvement obtained with more extensive procedures do not justify the increased morbidity, postoperative complications and higher mortality rate.

7. If one excludes the patients with contraindications listed in paragraph 4 of the conclusions, it is our opinion that thoracolumbar sympathectomy is indicated as a palliative procedure for hypertensive patients in class IV and probably in selected cases in class III. In our experience it is the most effective form of therapy available for such patients.

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Causes of Death in Hypertension*

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EARLY in the evolution of hypertensive heart disease the importance of examination of the ocular fundi was noted.[10,28] By comparing such findings with clinical observations Wagener and Keith,[31] and later Keith, Wagener and Kernohan,[11,14] were able to differentiate the malignant form of essential hypertension from the benign form. By further study in which particular attention was paid to the the arteriolar changes throughout the body resulting from hypertensive disease, Wagener and Keith[32] were able to develop a classification for essential hypertension. Wagener[29,30] also pointed out that retinal findings did not represent a fixed entity; a patient who on initial examination was considered to have hypertension, group 1 or 2, might at a later date show definite evidence of an added angiospastic factor and would then be considered to have hypertension, group 3 or 4. On the other hand, in certain individuals initially considered as having hypertension, group 3 and occasionally group 4, regression of the angiospastic features might occur and the hypertensive disease thus might revert to group 2 and even to group 1.

Numerous investigators[5,7,12,15,16,18,20,21,24,25] in the past twenty years have studied arteriolar changes in different organs and tissues of the body in benign and malignant hypertension. The evidence accumulated from these studies has substantiated the basic idea that essential hypertension, and especially malignant hypertension, is a diffuse arteriolar disease affecting all organs in varying degree; also that a definite correlation exists between the severity of hypertension and the degree of arteriolar involvement. Many investigators also have reported their findings relative to the final cause of death in essential hypertension.[1,2,19,22,23]

The association of hypertension and coronary sclerosis is more than a casual one. According to Bell and Clawson in approximately two-thirds of all clinical cases of coronary disease hypertension is associated, and Fahr has stated that 75 per cent is a conservative estimate for the number of patients with coronary disease who at some time have hypertension.

Blackford and Wilkinson found hypertension occurring twice as frequently in women as in men; however, the mortality rate after ten years was twice as great in men. Stein and Barnes also noted a more common occurrence of hypertension in women and found that hypertensive females survived longer than hypertensive males. The majority of patients having benign hypertension die after the age of fifty years, and the majority of patients having malignant hypertension die before reaching the age of fifty.[8,17]

Cardiac hypertrophy as a result of hypertension has been observed and discussed by practically all investigators who have written on hypertension. Stein and Barnes have concluded that the degree of cardiac hypertrophy appears to be closely related to the severity of hypertension but unrelated to duration of the disease.

SELECTION OF CASES AND METHOD OF STUDY

Although a total of 2,650 records of cases of hypertension which came to necropsy at the Mayo Clinic from 1924 to 1948 inclusive were reviewed, only 376 cases of primary or essential hypertension were considered as suitable for our study. Cases of hypertension in which there was

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a known etiologic factor, such as the hypertension associated with valvular heart disease, glomerulonephritis, polycystic disease of the kidneys and others, were excluded.

On the basis of examination of the ocular fundi the hypertension was classified into the four groups described by Keith, Wagener and Barker.[13,32] For our study there were 100 cases each of hypertension, groups 1, 2 and 4, and 76 cases of hypertension, group 3. As much individual variability as possible was eliminated by using cases only in which examination of the ocular fundi had been performed by one or the other of two ophthalmologists.

Patients having minimal to grade 1 retinal arteriolosclerosis and minimal to grade 1 narrowing of the arterioles were considered to have hypertension, group 1.[33] Patients who had generalized retinal arteriolosclerosis, grade 1 or 2, and generalized narrowing of the arterioles, grade 1 or 2 and occasionally grade 3, were considered to have hypertension, group 2. In some fundi there were areas of focal constriction and at times focal arteriolosclerosis. In an occasional fundus there were areas of hemorrhage. All the patients who had hypertension, group 3, had severe retinal arteriolar changes, generalized retinal arteriolosclerosis, grade 2 to 3, and generalized narrowing of the arterioles, grade 2 to 3. In many of the fundi there were focal constrictions in the arterioles and focal arteriolosclerosis. All patients had edema of the retina, cotton-wool patches and hemorrhages. Often residues of edema were noted in the form of macular stars or scattered punctate deposits. Patients whose hypertension was considered as group 4 had edema of the optic disks in addition to the retinitis described as indicative of hypertension, group 3.

The blood pressure of patients who had hypertension, group 1, was labile; during periods of rest it would return to normal. In an occasional instance there was evidence of cardiac or renal damage. The blood pressure of patients who had hypertension, group 2, was higher and there was less fluctuation. In most cases of hypertension, group 2, the blood pressure was lower at rest but rarely fell to normal levels. In many cases there was clinical and laboratory evidence of previous cardiac, renal or cerebral insufficiency. Some of the patients in this group originally had hypertension, group 1, but the condition had progressed over a period of years and later was classed as group 2. The blood pressure of patients with hypertension, group 3, was higher and more sustained; there was less fluctuation even when the patient was at rest. The majority of patients had definite evidence of diminished cardiac reserve, renal reserve and cerebral impairment. Decreased cardiac reserve was manifested by previous episodes of cardiac failure, or previous history and electrocardiographic findings compatible with coronary disease. In almost every instance there was clinical and roentgenologic evidence of cardiac enlargement. Renal impairment often was manifested by a low urinary specific gravity, albuminuria and, in some cases, casts and cellular elements in the urine. The level of urea in the blood was invariably elevated. The history and physical findings in some cases gave good evidence of a previous cerebral vascular accident; in others the symptomatology strongly suggested impending cerebral failure. Blood pressure of patients who had hypertension, group 4, was in most instances higher than that in the other three groups. In the majority of cases there was evidence of previous cardiac, renal and cerebral insufficiency.

In view of the fact that hypertension in some patients changed from one group to another during the course of the disease, they were considered to have hypertension of the group classified at the time of death. Since the change in group has in some instances been found to occur rapidly, only those cases were used in which a recent funduscopic examination had been made.

In addition to necropsy findings the clinical course was considered in determining the immediate cause of death in each of the 376 cases. In some instances a careful appraisal of all available information was necessary in order to make a final diagnosis. The cause of death in these cases fell into five categories: (1) congestive heart failure, (2) coronary disease, (3) cerebrovascular accident, (4) uremia and (5) all causes unrelated to hypertension. At necropsy in cases in which congestive heart failure was considered the cause of death, there was evidence of passive congestion of one or several organs or dilation of the chambers of the heart or both. In some cases there was hydrothorax or ascites. In many patients dying from other causes there also was evidence of varying degrees of heart failure. In these cases circumstances prevailing at the time of death were carefully considered. The

diagnosis of congestive failure was made only when the bulk of evidence was in its favor.

In cases in which death was due to coronary disease, death occurred rapidly with the patient presenting a picture of shock. At necropsy either recent thrombosis of a coronary artery with or without myocardial infarction or coronary sclerosis of sufficient degree to produce severe coronary insufficiency with or without myocardial infarction was found. In the cases in which there was severe coronary disease plus varying degrees of cardiac failure, the clinical course and the findings at necropsy were carefully appraised. The final classification depended on where the bulk of evidence lay. This difficult, but fortunately, small group has undoubtedly produced a small amount of error between the first two categories. This discrepancy, however, is eliminated if the two groups are combined. Also included here are two cases of myocardial infarction complicated by rupture of the myocardium.

TABLE I

CAUSES OF DEATH ACCORDING TO GROUP OF HYPERTENSION

Cause of Death	Total		Hypertension				
			Group 1, Cases or Per cent	Group 2, Cases or Per cent	Group 3		Group 4, Cases or Per cent
	No.	Per cent			No.	Per cent	
Congestive heart failure	98	26.1	21	26	30	39.5	21
Coronary disease	37	9.8	7	20	9	11.8	1
Cerebrovascular accident	56	14.9	9	17	14	18.4	16
Uremia	76	20.2	3	2	12	15.8	59
Other	109	29.0	60	35	11	14.5	3
Total	376	100.0	100	100	76	100.0	100

Cerebrovascular accident was listed as the cause of death only in cases of cerebral hemorrhage and cerebral infarction. Cases of ruptured congenital aneurysm were excluded because of the indefinite association between this condition and hypertension. The brain was examined at necropsy in all but six cases in which cerebrovascular accident was considered the cause of death. In three of these six cases the clinical picture was compatible with cerebral infarction, and in the other three cases it supported a diagnosis of cerebral hemorrhage.

In many cases in which uremia was considered the cause of death cardiac failure was associated but in most instances there was little difficulty in making a differential diagnosis.

Patients dying from causes unrelated to hypertension died from carcinoma, brain tumor, surgical complications, infection, blood dyscrasias and other less common causes.

In addition to the cause of death the associated conditions were studied also in relation to the primary cause of death and the group of hypertension. These consisted of congestive heart failure, coronary disease (coronary sclerosis with or without occlusion), evidence of cerebrovascular accidents, uremia or renal insufficiency. The coronary sclerosis was not considered significant unless there were areas with 25 per cent or more occlusion of the lumen. In some cases there was almost complete occlusion of the lumen and in some there was myocardial fibrosis and scarring as evidence of previous myocardial infarction. The criterion for renal insufficiency was a value for blood urea of more than 40 mg. per 100 cc. Other criteria were the presence of albuminuria and a low specific gravity and in some cases hyaline and granular casts in the urinary sediment.

RESULTS

Diffuse Arteriolar Disease with Hypertension, Group 1. The causes of death in each of the four hypertensive groups are recorded in Table I. In Table II the sex incidence is included. Only 40 of the 100 patients who had hypertension, group 1, died of causes related to hypertension. Congestive cardiac failure accounted for twenty-one of the forty deaths. Comprising this group were sixteen males and five females. Nine deaths were due to cerebrovascular accidents, all nine occurring in male patients. Of the seven patients dying of coronary disease, six were males. There were three deaths due to uremia. All were male patients. Other causes of death consisted of nine cases of brain tumor, eight of bronchopneumonia, eight of fatal pulmonary embolism, seven of carcinoma, six of peritonitis, five of ruptured cerebral aneurysm, two of blood dyscrasias and two of Hodgkin's disease. The remaining thirteen patients died of a variety of unrelated causes, various types of infection predominating.

Thirty-one (77.5 per cent) of the forty patients dying as a result of hypertension had clinico-pathologic evidence of impair-

ment of more than one type. (Table III.) Significant coronary disease was found in 82.5 per cent of the forty patients. In addition to the seven patients dying of coronary disease there were twenty-six who had a significant degree of coronary sclerosis.

Three patients, in addition to the nine dying of cerebrovascular accidents, had definite clinical evidence of previous strokes. The brain was not examined at necropsy in these three patients. The brain was examined in seven of the nine patients dying

TABLE II

SEX INCIDENCE ACCORDING TO CAUSE OF DEATH AND GROUP OF HYPERTENSION

Cause of Death	Total (376 patients)				Group 1		Group 2		Group 3		Group 4	
	Males		Females		Males	Females	Males	Females	Males	Females	Males	Females
	No.	Per cent	No.	Per cent								
Congestive heart failure	71	26.7	27	24.5	16	5	23	3	16	14	16	5
Coronary disease	26	9.8	11	10.0	6	1	14	6	5	4	1	0
Cerebrovascular accident	39	14.7	17	15.5	9	0	11	6	9	5	10	6
Uremia	60	22.5	16	14.5	3	0	1	1	7	5	49	10
Other causes	70	26.3	39	35.5	40	20	19	16	8	3	3	0
Total	266	100.0	110	100.0	74	26	68	32	45	31	79	21

TABLE III

DEATHS AS A RESULT OF HYPERTENSION IN CASES OF HYPERTENSION, GROUP 1

Secondary Conditions	Cause of Death				Total
	Congestive Heart Failure	Coronary Disease	Cerebrovascular Accident	Uremia	
Congestive heart failure	**5***	0	0	1	6
Coronary disease	7	**3**	6	1	17
Cerebrovascular accident	0	1	**1**	0	2
Uremia	0	0	0	..	0
Congestive heart failure and coronary disease	0	0	1	1	2
Congestive heart failure and cerebrovascular accident	0	1	0	0	1
Congestive heart failure and uremia	0	2	0	0	2
Coronary disease and cerebrovascular accident	1	0	0	0	1
Coronary disease and uremia	8	0	1	0	9
Total	21	7	9	3	40
Additional cases in which condition was found but was not main cause of death	6	26	3	11	31†

* Numbers in bold face indicate cases in which no secondary conditions were noted.

† These do not total correctly because the same patient sometimes had three lesions.

In addition to the twenty-one patients dying from cardiac failure six others had clinically significant degrees of congestive failure.

as a result of cerebrovascular accidents. In four instances death was due to massive hemorrhage and in the remaining three there was cerebral infarction. In the two

cases in which the brain was not examined the clinical picture was typical for cerebral infarction.

Uremia was the cause of three deaths. Eleven additional patients had varying degrees of clinically significant renal insufficiency. This total of fourteen patients is equal to 35 per cent of the forty patients dying as a result of hypertension in this group.

Diffuse Arteriolar Disease with Hypertension, Group 2. In hypertension, group 2, death in sixty-five patients was due to causes related to hypertension and in thirty-five to other causes. Again congestive heart failure accounted for the majority of deaths. (Tables I and IV.) Of the thirty-five patients dying of causes unrelated to hypertension eight died of brain tumor, four each died of carcinoma and peritonitis, three each of ruptured cerebral aneurysm and pulmonary embolism and two of bronchopneumonia. The remaining eleven patients died of miscellaneous causes. The sex incidence is given in Table II.

Fifty-seven patients (87.7 per cent) of the sixty-five dying as a result of hypertension had significant clinico-pathologic impairment of more than one system. Seven patients had significant clinico-pathologic impairment of all the four systems affected by hypertension. Twenty-five patients had significant impairment of various combinations of three systems. (Table IV.)

TABLE IV

DEATHS AS A RESULT OF HYPERTENSION IN CASES OF HYPERTENSION, GROUP 2

Secondary Lesions	Cause of Death				Total
	Congestive Heart Failure	Coronary Disease	Cerebrovascular Accident	Uremia	
Congestive heart failure	**1***	1	1	1	4
Coronary disease	3	**6**	8	1	18
Cerebrovascular accident	0	3	**1**	0	4
Uremia	2	5	0	**0**	7
Congestive heart failure and uremia	0	2	0	0	2
Coronary disease with cerebrovascular accident	3	0	0	0	3
Coronary disease and uremia	12	0	3	0	15
Cerebrovascular accident and uremia	2	3	0	0	5
Coronary disease, uremia, cerebrovascular accident and congestive heart failure	3	0	4	0	7
Total	26	20	17	2	65
Additional cases in which condition was found but was not cause of death	9	37	14	36	57†

* Numbers in bold face indicate cases in which no secondary conditions were found.

† These do not total correctly because the same patient sometimes had three lesions.

As in hypertension, group 1, significant coronary artery disease again predominated. It was present in fifty-seven patients (87.7 per cent of the sixty-five dying as a result of hypertension). Twenty-three of thirty-seven patients in whom it was a secondary lesion had a severe degree of coronary sclerosis and evidence of previous myocardial infarction. Myocardial infarction was evident in all twenty patients dying of coronary disease; in twelve there was recent coronary artery thrombosis. Two patients in this group died of cardiac rupture and intrapericardial hemorrhage. Both patients had recent thrombosis of the anterior descending branch of the left coronary artery and anterior left ventricular myocardial infarction. In both cases rupture was at the apex of the left ventricle.

Renal insufficiency occurred in 58.5 per

cent of the sixty-five patients dying of causes related to hypertension.

Fourteen patients, in addition to the seventeen dying of cerebrovascular accidents, had clinico-pathologic evidence of cerebral insufficiency. The brain was examined at necropsy in seven of the fourteen cases and areas of previous infarction were found. In the remaining seven cases clinical histories and findings clearly indicated previous cerebrovascular accidents. Cerebral infarction accounted for eleven of the seventeen deaths due to cerebrovascular accidents; the six remaining deaths were due to cerebral hemorrhage. The cases of cerebral hemorrhage were equally divided between the sexes. Of the cerebral infarctions three occurred in females and eight in males. In all seventeen cases the brain was examined at necropsy and the final diagnosis was made from this examination.

Diffuse Arteriolar Disease with Hypertension, Group 3. Sixty-five of the total of seventy-six patients who had hypertension, group 3, died of causes related to hypertension. (Tables I, II and V.) Congestive heart failure again accounted for the largest number of deaths, 39.6 per cent of the total. Of the conditions not associated with hypertension bronchopneumonia was the cause of death of three patients, carcinoma of two, and ruptured cerebral aneurysm, ruptured abdomino-aortic aneurysm, brain tumor, peritonitis, empyema and obstructive jaundice with hepatic insufficiency each caused death of one patient.

TABLE V

DEATHS AS A RESULT OF HYPERTENSION IN CASES OF HYPERTENSION, GROUP 3

Secondary Lesions	Cause of Death				Total
	Congestive Heart Failure	Coronary Disease	Cerebro-vascular Accident	Uremia	
Congestive heart failure	**1***	2	0	4	7
Coronary disease	4	**0**	4	3	11
Cerebrovascular accident	0	2	**2**	1	5
Uremia	7	1	0	**1**	9
Congestive heart failure and coronary disease	0	0	0	3	3
Congestive heart failure and uremia	0	3	2	0	5
Coronary disease and uremia	15	0	6	0	21
Coronary disease, uremia, cerebrovascular accident and congestive heart failure	3	1	0	0	4
Total	30	9	14	12	65
Additional cases in which condition was found but was not cause of death	15	38	7	38	61†

* Numbers in bold face indicate cases in which no secondary conditions were found.

† These do not total correctly because the same patient sometimes had three lesions.

Sixty-one (93.8 per cent) of the sixty-five patients dying as a result of hypertension, group 3, had significant impairment of more than one system. There were twenty-nine patients with impairment of three systems and four patients with all four systems affected. (Table v.)

Seventy-seven per cent of the sixty-five patients dying of the complications of hypertension had significant renal insufficiency.

There was a definite decline in the frequency of significant coronary artery disease occurring in patients in this group. Only 72.3 per cent of the sixty-five patients dying of hypertensive causes had this lesion. At necropsy there was evidence of myocardial infarction in all nine patients dying of coronary disease, and in four cases there was a recent thrombus occluding one of the coronary vessels.

Congestive heart failure was found in fifteen patients in addition to the thirty patients dying of this condition.

In addition to the fourteen patients dying of cerebrovascular accidents seven presented evidence of cerebral impairment. In six the brain was examined at necropsy and old areas of infarction were present. In the seventh case there were residua of a previous hemiplegia. In all but one of the fourteen cases in which cerebrovascular accident was considered the cause of death the final diagnosis was made by examining the brain at necropsy. In the one case in which the brain was not examined the clinical course was compatible with cerebral hemorrhage. Cerebral hemorrhage occurred in ten cases; in three in female patients and seven in males. The four remaining cases of cerebral infarction were divided equally between the sexes.

TABLE VI

DEATHS AS A RESULT OF HYPERTENSION IN CASES OF HYPERTENSION, GROUP 4

Secondary Lesions	Cause of Death				Total
	Congestive Heart Failure	Coronary Disease	Cerebrovascular Accident	Uremia	
Congestive heart failure	**2***	0	1	16	19
Coronary disease	1	0	3	3	7
Cerebrovascular accident	0	0	**1**	2	3
Uremia	2	1	4	**8**	15
Congestive heart failure and coronary disease	0	0	0	12	12
Congestive heart failure and cerebrovascular accident	0	0	0	4	4
Congestive heart failure and uremia	0	0	1	0	1
Coronary disease and cerebrovascular accident	0	0	0	5	5
Coronary disease and uremia	13	0	2	0	15
Cerebrovascular accident and uremia	1	0	0	0	1
Coronary disease, cerebrovascular accident, congestive heart failure and uremia	2	0	4	9	15
Total	21	1	16	59	97
Additional cases in which condition was found but was not cause of death	47	54	23	30	86†

* Numbers in bold face indicate cases in which no secondary conditions were found.

† These do not total correctly because the same patient sometimes had three lesions.

Diffuse Arteriolar Disease with Hypertension, Group 4. Of the 100 patients who had hypertension, group 4, ninety-seven died as a result of the hypertension. (Tables I, II and VI.) Uremia was the cause of death in fifty-nine instances (59 per cent). Of the three patients not dying as a result of hypertension, one died of hemorrhage from a chronic duodenal ulcer, one died after rupture of an aneurysm of the circle of Willis and the other patient of a dissecting aneurysm of the aorta with rupture into the pericardium.

Eighty-six (88.7 per cent) of the ninety-seven patients dying hypertensive deaths had more than one system impaired. (Table VI.) There were thirty-eight patients with significant impairment of three systems and fifteen patients with all four systems affected. Renal insufficiency was the predominating feature of this group; eighty-nine (91.7 per cent) of the ninety-seven patients had varying degrees of renal insufficiency. (Table VI.) Coronary disease which predominated in the milder groups decreased rather markedly; fifty-five (56.7 per cent) of the ninety-seven patients had evidence of coronary sclerosis. Forty-seven patients had cardiac decompensation besides the twenty-one who died as a result of cardiac failure.

There were twenty-three patients with cerebral impairment besides the sixteen patients succumbing to cerebrovascular accidents. The brain was examined at necropsy in twenty of the twenty-three patients and in every case small areas of old infarction or hemorrhage was found. In most cases there were multiple lesions in the brain. The clinical findings were definite in the three cases in which the brain was not examined. The sixteen deaths due to cerebrovascular accidents were equally divided between cerebral infarction and cerebral hemorrhage. Of the eight patients dying of cerebral infarction there were three females and five males; of the eight dying of hemorrhage there were also three females and five males. The findings were confirmed by necropsy examination of the brain in thirteen instances. In the other three cases the clinical course was compatible with cerebral hemorrhage in two and cerebral infarction in one.

TABLE VII

AGE AT DEATH ACCORDING TO GROUP AND SEX OF PATIENT

Age at Death, (yr.)	Total		Group 1		Group 2		Group 3		Group 4	
	No.	Per cent	Males	Females	Males	Females	Males	Females	Males	Females
20–29	7	1.9	0	0	0	0	0	1	3	3
30–39	30	8.0	1	0	2	0	4	2	16	5
40–49	69	18.4	6	4	4	5	13	7	22	8
50–59	125	33.2	23	9	25	9	16	12	27	4
60–69	97	25.8	27	8	27	9	9	6	10	1
70–79	46	12.2	15	5	10	9	3	3	1	0
80–89	2	0.5	2	0	0	0	0	0	0	0
Total	376	100.0	74	26	68	32	45	31	79	21
Mean by sex			62.1	60.5	60.1	61.3	53.6	53.7	48.1	42.6
Highest age (yr.)	84		84	77	79	77	77	74	75	62
Lowest age (yr.)	22		39	44	30	40	37	26	23	22
All cases	55.8		61.7		60.5		53.6		47.0	

AGE AND SEX

In Table VII the age at death, according to group, the mean age at death and the sex incidence are recorded. By referring to this table one can see that the oldest patient in this series was eighty-four years of age and the youngest was twenty-two years of age with a mean age of 55.8 years. The youngest patient was a female, who had hypertension, group 4, while the oldest was a male who had hypertension, group 1. The difference in the age at death in the various groups is rather significant. Of the 100 patients in group 1, eighty-nine (89 per cent) were fifty years of age or older, and all but two of these died between the age of fifty and seventy-nine years. The mean age of patients who had hypertension, group 1, at death was 61.7 years.

In group 2, as in group 1, eighty-nine patients (89 per cent) died at fifty years of age or more, and all eighty-nine died between the ages of fifty and seventy-nine. Seventy patients, however, died between the ages of fifty and sixty-nine. In the cases of hypertension, groups 1 and 2, there was little difference between the male and female mean age at death, and little or no difference between the ages of those dying of causes related to hypertension and those dying of other causes.

The first really significant change is seen in the cases of hypertension, group 3. The mean age at death was 53.6 years. There was little difference between the male and female mean age at death. Sixty-three (82.9 per cent) of the patients died between the

ages of forty and sixty-nine. Forty-nine (64.4 per cent) died at age fifty years or more.

Another significant change is seen in the cases of hypertension, group 4. The mean age at death was forty-seven years. The mean age of death for the male patients was 48.1 years; for the female patients it was 42.6 years. Approximately 50 per cent of the male patients were 50 or more years of age at the time of death whereas only approximately 24 per cent of the female patients were fifty or more years of age. Eighty-two patients (82 per cent) died between the ages of thirty and fifty-nine years, and only forty-three (43 per cent) died at the age fifty or more years.

CARDIAC WEIGHTS

The weight of the heart recorded is the absolute weight at the time of necropsy. In every instance the heart was enlarged.[26] For the entire series of 376 patients the mean weight of the heart was 551.8 gm. The lightest heart weighed 200 gm. and the heaviest weighed 1,100 gm. The mean weights and extremes of patients who had hypertension of various groups and for males and females are given in Table VIII.

TABLE VIII

WEIGHT OF THE HEART ACCORDING TO GROUP OF HYPERTENSION AND SEX OF PATIENT

Weight of the Heart, (gm.)	Total		Group 1		Group 2		Group 3		Group 4	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
200–299	0	1	0	1	0	0	0	0	0	0
300–399	18	37	10	14	5	18	2	2	1	3
400–499	56	29	26	6	13	8	9	7	8	8
500–599	78	26	23	5	19	3	7	14	29	4
600–699	64	14	10	0	17	3	12	5	25	6
700–799	30	2	4	0	8	0	6	2	12	0
800–899	14	0	0	0	4	0	7	0	3	0
900–999	2	1	0	0	1	0	1	1	0	0
1,000–1,099	3	0	1	0	1	0	1	0	0	0
1,100–1,199	1	0	0	0	0	0	0	0	1	0
Total	266	110	74	26	68	32	45	31	79	21
Mean by sex	586.1	468.7	522	393.3	590	417.7	633.3	551	616.1	519
Lightest	317	200	317	200	340	310	338	305	386	356
Heaviest	1,100	958	1,070	594	1,030	690	1,030	958	1,100	692
All cases	551.8		488.4		534.8		600		595.7	

COMMENT

The number of deaths resulting from hypertension, groups 1, 2 and 3, in this series appear somewhat lower than those in some series reported in the literature. Those due to hypertension, group 4, compare quite closely. The reason for this difference is due to selection.[9] Only those cases were included in this study in which the retina had been examined and which had come to necropsy at the Mayo Clinic. Many of the patients dying of causes not related to hypertension succumbed to carcinoma, brain tumors and postoperative complications. In these cases hypertension was an incidental finding and was in most instances not known prior to admission to the clinic. Of the 276 patients comprising the first three groups, 106 died of causes unrelated to hypertension. If the remaining 170 patients who died of causes related to hypertension are considered, the results of this study are in general agreement with the reports in the literature. (Table I.)

It has been observed that the hypertension of many patients changes from one group to another during the course of the illness. In some cases it may even progress to group 4 and later revert back to one of

the other groups. In this study an attempt was made to correlate the change of hypertension from one group to another with duration of life after onset of symptoms, progression of the disease and prognosis. Unfortunately, because of selection and in some cases lack of sufficient data, such correlation was not possible.[3]

Keith and his co-workers[14] in one of their early reports stressed the fact that patients with malignant hypertension do not as a rule die from failure of one vital organ but rather from simultaneous failure of several. In the present study this feature was observed not only among patients dying of hypertension, group 4, but also among those dying of benign hypertension. In fact, there was not a very marked difference between the various groups. This made it rather difficult in some instances to determine the actual cause of death, especially in those cases in which severe coronary sclerosis and congestive heart failure were present.

It is interesting to note that the highest percentage of association of moderate to severe coronary sclerosis with hypertension (87.7 per cent) was seen in the cases of hypertension, group 2, and the lowest (56.7 per cent) in the cases of hypertension, group 4. This is most likely due to the fact that patients who have hypertension, group 4, die before severe coronary sclerosis can develop. These figures are derived only from those patients dying of causes related to hypertension.

Renal insufficiency and its association with hypertension often has been the subject for extensive discussion. In this study there was a definite correlation between this and the severity of hypertension. When only those patients dying from causes related to hypertensive deaths were considered, the incidence of association of renal insufficiency varied from 35 per cent in cases of hypertension, group 1, to 91.7 per cent in hypertension, group 4.

In accordance with the observations made by others uremia was the chief cause of death among the patients with hypertension, group 4; 59 per cent died of uremia in our series. At necropsy twenty-two of the fifty-nine (37.3 per cent) had uremic pericarditis. The mean age of the patients dying of uremia was 45.3 years; the mean age for all the patients who had hypertension, group 4, was forty-seven years. The mean value for blood urea for the fifty-nine uremic patients was 290 mg. per 100 cc. with a range from 80 to 651 mg. Serum creatinine determinations were available in fifty-two of the fifty-nine cases. The mean values for serum creatinine was 12.2 mg. per 100 cc. with a range from 3.0 to 35.2 mg.

A total of fifty-six patients of the entire series of 376 died of cerebrovascular accidents. In all but six instances the brain was examined at necropsy. In these six cases the clinical picture was conclusive. Cerebral hemorrhage and encephalomalacia occurred in twenty-eight cases each. In Bell and Clawson's series the brain was examined in seventy-six of eighty-one cases. Cerebral hemorrhage was present in fifty instances and encephalomalacia in twenty-six.

The brains were examined at necropsy in the twenty cases in which the patients who had had hypertension, group 4, and prior to death had had clinical evidence of cerebral impairment as well as in the cases in which the patients died of cerebral lesions. In each instance the postmortem findings were those described by Rosenberg, that is, intracerebral and extracerebral edema and multiple miliary hemorrhages or infarcts or both.

In this study there was a definite relationship between the mean age at death and the respective groups. (Table VII.) The majority of patients with hypertension, groups 1 and 2, died at a later age than did patients who had hypertension, groups 3 and 4. Eighty-nine per cent of the former died at age fifty years or more whereas only 64.4 per cent of patients with hypertension, group 3, and 43 per cent of group 4 patients lived that long.

The sex ratio in those patients coming to necropsy during the period of this report was 2.3 males to 1 female. Differences in

sex ratio in the respective groups may well be a result of selection; consequently no definitive conclusions can be drawn between the sex incidence of each group.

A relation can be seen between the weight of the heart and the severity of the hypertension. (Table VIII.) The mean weight of the heart in cases of hypertension, group 1, was 488.4 gm.; of group 2, 534.8 gm.; of group 3, 600 gm., and of group 4, 595.7 gm. The mean for the entire series was 551.8 gm. An attempt was made to correlate the weight of the heart with the known duration of the hypertension but it was impossible to show any correlation.

SUMMARY AND CONCLUSIONS

For this study 376 cases of primary hypertension were selected from 2,650 consecutive cases of hypertension coming to necropsy at the Mayo Clinic during twenty-four years. The main basis for selection was examination of the ocular fundi. The classification of hypertension devised by Wagener and Keith was used. One hundred patients each had hypertension, groups 1, 2 and 4, and seventy-six of group 3. The final cause of death was determined in each case.

Of 100 patients who had hypertension, group 1, forty died of causes related to hypertension; congestive heart failure and coronary disease were causes in twenty-eight cases (28 per cent), cerebrovascular accidents in nine cases (9 per cent) and uremia in three cases (3 per cent).

Of 100 patients who had hypertension, group 2, sixty-five died of causes directly related to hypertension. Congestive heart failure and coronary disease were present in forty-six cases (46 per cent), cerebrovascular accidents in seventeen cases (17 per cent) and uremia in two cases (2 per cent).

Of seventy-six patients who had hypertension, group 3, sixty-five died of causes related to hypertension. There were thirty-nine patients (52.4 per cent) who died of congestive heart failure or coronary disease, fourteen (18.4 per cent) who died of cerebrovascular accidents and twelve (15.8 per cent) of uremia.

Ninety-seven patients died of causes related to hypertension of 100 patients who had hypertension, group 4. Twenty-two (22 per cent) died of cardiac failure or coronary disease, sixteen (16 per cent) died of cerebrovascular accidents and fifty-nine (59 per cent) died of uremia.

The incidence of a significant degree of associated coronary sclerosis was highest in patients who had hypertension, groups 1 and 2. It was noted in 82.5 and 87.7 per cent, respectively, of patients dying of hypertensive causes in these groups. There was a marked decrease in this association in patients who had hypertension, group 4 (56.7 per cent).

Associated renal impairment was definitely correlated to the severity of hypertension; it occurred in 35 per cent of patients dying of causes related to hypertension, group 1, and in 91.7 per cent of patients who died of causes related to hypertension, group 4.

A total of fifty-six patients died of cerebrovascular accidents, twenty-eight each of cerebral hemorrhage and encephalomalacia.

There was a definite relationship between the mean age at death and the severity of hypertension; in cases of hypertension, group 1, it was 61.7 years and in those of hypertension, group 4, 47 years.

Although there was a correlation between the weight of the heart and the severity of hypertension, no correlation could be shown between the weight of the heart and duration of known hypertension.

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Review

Spontaneous Rupture of a Papillary Muscle of the Heart

Review with Eight Additional Cases

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RUPTURE of a papillary muscle of the heart occurs so rarely that reliable criteria justifying other than a conjectural diagnosis have not been established. The diagnosis had always been made by the pathologist until the last year when Davison[1] suspected the correct antemortem diagnosis. In two other cases (cases VII and VIII) in which the correct diagnosis was suspected before death, based upon criteria which differentiated the rupture from perforation of the interventricular septum, the data have been made available.† These three are apparently the only reported instances of correct diagnosis before death.

Only twenty-nine cases of spontaneous rupture of a papillary muscle are on record. The majority have been shown to follow myocardial infarction. We wish to report eight additional cases.‡ One case is noteworthy because of its interesting cause: It is the first instance to result from necrotizing periarteritis. In the other seven cases rupture followed myocardial infarction.

The data from the combined thirty-seven records are analyzed. Criteria are suggested which in certain instances should permit logical suspicion of the correct diagnosis if the patient is under close observation. Certain diagnostic criteria are emphasized and an additional etiologic factor is recorded.

Stevenson and Turner[2] reviewed the recorded cases in 1935; they added one case to the previously recorded nineteen. Since then Hausen-Faure and Hasenjager[3] have added two, Moragues[4] one, Lowry and Burn[5] one, Lipscomb[6] one, Davison[1] three and Foster[7] one. Our eight additional cases make a total of thirty-seven instances. Davison's table gives the essential data with the exception of Foster's case and our eight additional cases.

Etiology. Cardiac infarction is by far the most important cause of rupture of a papillary muscle. It was the cause twenty-seven times; once coronary arterial disease without demonstrable postmortem coronary arterial occlusion or myocardinal infarction was found;[5] in one instance a patient with clinical angina pectoris and a ruptured papillary muscle had apparently normal coronary arteries.[8] The cause in two instances is unknown,[9,10] Twice ulcerative endocarditis was responsible. In one patient the spirochetes of syphilis were demonstrated in the papillary muscle and it was believed that this accounted for the necrosis and rupture. A similar lesion might possibly have been a factor in the first case on record, that of Merat's patient in 1803 who had an associated aneurysm of the aorta.[11]

A papillary muscle of the left ventricle

† I wish to acknowledge the kindness of Drs. Francis C. Wood (Cases VII and VIII), William A. Jeffers (Case VIII), Thomas M. Kain, Jr. (Case VII), and C. C. Wolferth, of Philadelphia, in furnishing the data on these two cases.

‡ Only two cases were personally observed. The data in the other six cases were included through the courtesy of Drs. Matthew Brown (Case VI), Alvin G. Foord (Cases V and VI), C. M. Hughes (Case V), R. E. Hope (Case III), James E. Kahler, Julius Kahn (Case II), E. C. Rosenow, Jr. (Case V), Edward Shapiro (Case II) and C. E. Stehley (Case I).

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was involved in all but two patients; both had vegetative endocarditis. In these two the papillary muscle of the right ventricle was ruptured. In the instances in which the particular muscle involved was mentioned the posterior muscle was ruptured in nineteen, the anterior in eight, and in a most extraordinary case described by Nicod in 1834,[10] both muscles were ruptured; the report of the cause in this latter case is obscure.

Type of Murmur. In twenty-two instances murmurs were noted. In three other patients, including Cases III and V of our report, what was thought to be a friction rub was noted and in another the diagnosis "pericarditis" would imply that a rub was heard. Lowry and Burn[5] considered the loud pseudofriction rub in their patient to be produced by tangling of the end of the torn muscle in the twisted chordae tendineae. In nine of the thirty-seven cases of spontaneous rupture the end of the torn muscle was similarly caught. In six loud murmurs were heard, in two pseudofriction rub and in one no murmur was heard. In eight of the twenty-seven cases in which the particular muscle was mentioned the anterior papillary muscle of the left ventricle was ruptured. Moragues[4] suggested that patients with rupture of the anterior muscle had an apparently greater tendency to die with acute pulmonary edema than did those with rupture of the posterior muscle. However, this is not corroborated by Davison,[1] and in six of our eight cases, regardless of the muscle involved, pulmonary edema developed rapidly. Irregularity of the heart action was mentioned in eight instances. The type of irregularity was identified as auricular fibrillation twice but was not identified in the other instances.

CASE REPORTS

CASE I. A. S., a man aged fifty-seven, was admitted to St. Vincent's Hospital on January 31, 1946. Ten days before pain, throbbing in character, had developed in the left gluteal region. It became so severe that he consulted a doctor the next day. The pain was diagnosed as sciatic neuritis but because of fever the patient was given sulfonamides, the amount of which is not known. The fever persisted and the pain became so severe that the patient was admitted to the hospital. Examination revealed an apparently seriously sick man with a temperature of 102°F., pulse 120 and respirations 22. There was an area of marked tenderness near the left hip made much worse by movement. A tentative diagnosis of osteomyelitis of the ilium with abscess formation was made.

The past medical history was significant. In September, 1939, he had been in another hospital for four months suffering with osteomyelitis of the right thumb following an injury at work. Abscesses had developed involving the left shoulder, the upper left arm and the right lumbar area. A superficial lumbar abscess was operated upon twice and a psoas abscess was drained. Blood cultures on six successive days were negative. Guinea pig inoculations were also negative. The patient was discharged, afebrile, December 20, 1939. There was no history of any intervening illness between 1939 and the time of his present illness.

On February 2, 1946, a needle was inserted in the fluctuant area in the left gluteal region and purulent material was obtained. An incision was made and approximately 150 cc. of pus were obtained; a growth of Bacillus pyocyaneus was obtained from this pus. The initial blood count revealed hemoglobin 15 gm. per cent, 4,430,000 red blood cells and 15,000 white blood cells, with neutrophils 92 per cent, of which 59 per cent were non-filamented; there were no eosinophils at any time. The urinalysis on February 1st revealed 2 plus albumin, a few hyaline and granular casts and 5 to 7 pus cells per high power field; no red blood cells were present. The fever ceased to spike after evacuation of the abscess but continued slightly elevated to 100° to 100.4°F. for three weeks. Since admission left and right congestive heart failure had gradually developed, with rales in his chest, dyspnea and edema of the legs which gradually extended into the sacral region. The vital capacity on February 17th was 1.2 L. An electrocardiogram revealed no significant abnormalities. Roentgenogram of the chest on February 5th indicated a definite increase in the density of both lung fields due to peribronchial infiltration. On February 23rd there was moderate edema of the prepuce and the scrotum. A "snapping" quality to the heart tones was noted; no murmurs were present. The next day, the patient's thirty-fourth day of

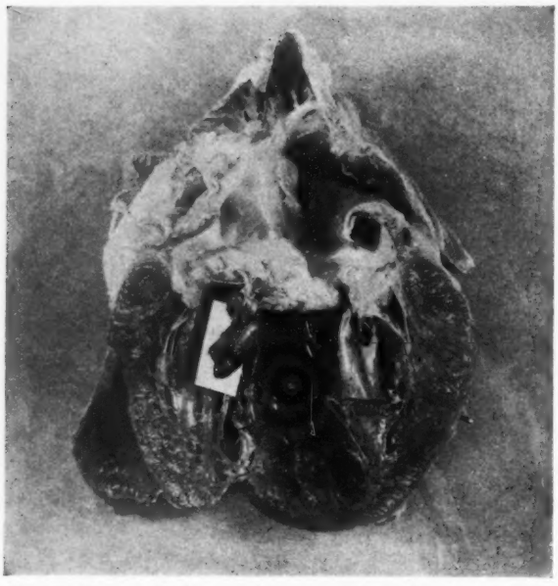

FIG. 1. Case 1. Left ventricle opened to show ruptured anterior papillary muscle to left, its basal end covered by firm clot. (The apical end of the ruptured muscle has been removed for section as has a block from the posterior papillary muscle as shown at right.) Note twisted chordae tendineae.

illness, sudden extreme dyspnea and cough developed with diffuse pulmonary edema. At this time a harsh systolic murmur of moderate intensity (grade 3) appeared at the apex. That night the heart murmur was much louder (grade 4 intensity) and was heard all over the precordium; the pulmonary edema was much worse. The patient died the next morning, February 24, 1946, at 10:20 A.M., twenty-four hours after the sudden development of the systolic murmur.

The significance of the sudden appearance of the loud systolic murmur was discussed. It was mentioned that such a murmur could occur with rupture of the interventricular septum in myocardial infarction or it could follow destruction of the chordae tendineae due to valvular vegetations. These diagnoses seemed untenable. No evidence had been present of endocarditis and the blood cultures had been negative.

Necropsy was performed by Dr. James E. Kahler within two hours of the time of death. The findings were as follow: There was an area of osteomyelitis in the anterior surface of the left ilium. The osteomyelitis was purulent in type, microscopically, and Staphylococcus aureus was recovered by culture. (Postmortem cultures of the blood were sterile.)

The heart weighed 330 gm. (Fig. 1.) It was an extremely soft and flabby organ with a reddish brown external appearance. The myocardium of the left ventricle was mottled with yellowish to gray ill defined areas which superficially resembled infarction but which when sectioned were very soft, suggesting an inflammatory change much older than the history indicated. The septum was similarly mottled and soft but the muscle of the right side of the heart was homogeneously reddish brown. There was moderate dilatation of all cardiac chambers. In the left ventricle there was complete rupture of the anterior papillary muscle, its basal end covered with a firm reddish thrombus while the apical end was rough, irregular and ragged. On cross section this papillary muscle was bright yellow in color and markedly decreased in consistency. The posterior papillary muscle had a similar appearance on section but was unruptured. The endocardium throughout was smooth and glistening and the valves were normal in appearance. The coronary arteries were only slightly sclerotic and contained no evidence of recent or old thrombosis. Microscopic sections of the papillary muscle demonstrated acute degenerative changes in the muscle fibers with bright red staining of the sarcoplasm, loss of striations and in many instances of nuclear staining. Only an occasional leukocyte was found infiltrating between the muscle fibers, the process being too acute for an inflammatory exudate to have developed to any great extent. The small arterioles seen within the papillary muscle contained a variety of changes consisting of marked intimal proliferation, complete loss of internal elastic membrane, some necrosis of the media with sparse leukocytic infiltration and marked exudation in the adventitia of polymorphonuclear leukocytes, lymphocytes, plasma cells and histiocytes. (Fig. 2.) Sections of the mottled areas of the myocardium revealed similar changes.

The kidneys had adherent capsules and scarred surfaces. The cortices were narrowed but clearly defined. Microscopically, there was a moderately active chronic pyelonephritis. Microscopic sections revealed many typical periarteritic changes in the liver and in the wall of the urinary bladder although there were no gross changes in these organs to suggest periarteritis. In none of the perivascular foci was more than an occasional eosinophil seen. (Fig. 3.)

The anatomic diagnoses were as follows: (1) periarteritis nodosa involving principally the vessels of the heart, the liver and the urinary

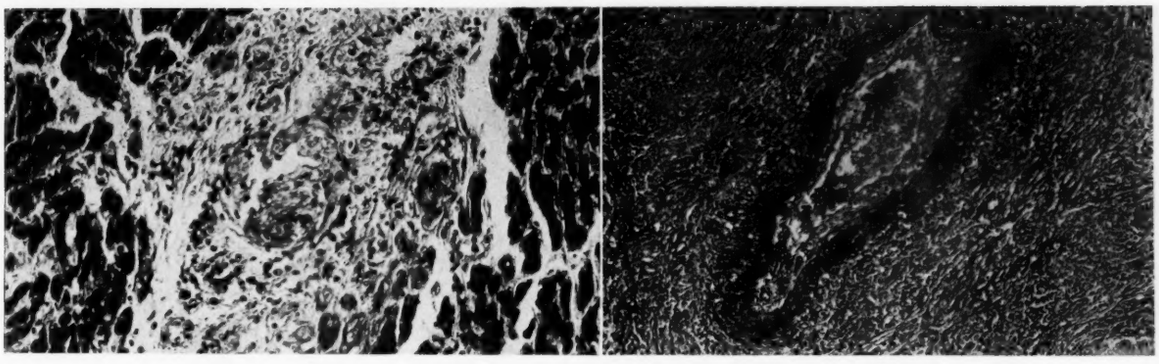

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FIG. 2. Case I. Photomicrograph of section of ruptured papillary muscle. In center: an arteriole with lumen nearly occluded by partially degenerated thrombus and normal structures of wall obscured by infiltrating leukocytes and macrophages. The dark-staining issue at each side of the photograph represents necrotic myocardial fibers.
FIG. 3. Case I. Photomicrograph of section of liver showing arteriole in portal triad the lumen of which is filled with thrombus; the media are necrotic, the adventitia densely infiltrated and widened by leukocytes and macrophages. A portion of bile duct appears at the lower right.

bladder; (2) multiple acute infarctions of the myocardium with rupture of the anterior papillary muscle and acute congestive heart failure; (3) osteomyelitis of the left ilium with iliopsoas and gluteal abscesses; (4) chronic pyelonephritis and (5) organizing pneumonia.

CASE II. P. J. O., a seventy-six year old male, was admitted to the Hospital of the Good Samaritan, Los Angeles, August 16, 1940, with a history of chills and fever of one week's duration. He gave a history of high blood pressure for an indefinite period. The blood pressure on admission was 182 systolic and 100 diastolic. The heart was enlarged to the left but murmurs were not heard. A few rales were heard in the bases of both lungs. The patient's temperature was 104°F. The next day after administration of sulfapyridine, 15 gr. every four hours, the temperature became normal, the blood pressure 120 systolic and 60 diastolic and the pulse 72. He was discharged August 19th with a diagnosis of fever of undetermined origin and hypertensive cardiovascular disease.

The patient was readmitted in coma on September 11th; he had had repeated chills since his discharge. The blood pressure was unobtainable. The details of the heart sounds were masked because of the loud respiratory sounds. The breath sounds were loud and harsh with many wheezes and coarse rales. The abdomen was distended but with no rigidity. There was a suggestion of a fluid wave. The blood count revealed 33,000 leukocytes. On September 13th a note read, "Moribund. The pulse and blood pressure are not obtainable. The chest is filling up." On September 13th an electrocardiogram revealed right bundle branch block. The patient died on September 14, 1940.

At necropsy the heart was found to be considerably enlarged, weighing 560 gm. It was soft and flabby. When the left ventricle was opened, the anterior papillary muscle of the mitral valve was found ruptured near the wall of the ventricle. The chordae tendineae attached to it were markedly twisted. The torn surface was covered by a blood clot. The anterior wall of the ventricle around the attachment of this muscle was softened and somewhat yellowish. The left anterior descending artery was sclerotic but not narrowed or occluded. A thrombus could not be found in any of its branches although some of the branches were markedly narrowed. A branch of the left circumflex artery leading into the anterior surface was almost completely occluded by sclerosis. The right coronary artery was widely patent. The mitral and aortic valves were essentially normal. The base of the aorta contained some small yellow plaques.

The liver showed dense adhesions completely covering the gallbladder. When these adhesions were cut away, the gallbladder was seen to be ruptured anteriorly and a considerable amount of slightly bile-streaked pus escaped. The gallbladder was greatly enlarged. The anterior wall was thickened, the posterior wall was honeycombed and there were many perforations leading into a space between the gallbladder and the liver. In the lower end of the gallbladder there was a large cylindrical stone measuring 2.5 cm. in length and 2.0 cm. in thickness. Small abscesses were found in the liver beneath the bed of the gallbladder. The common and hepatic

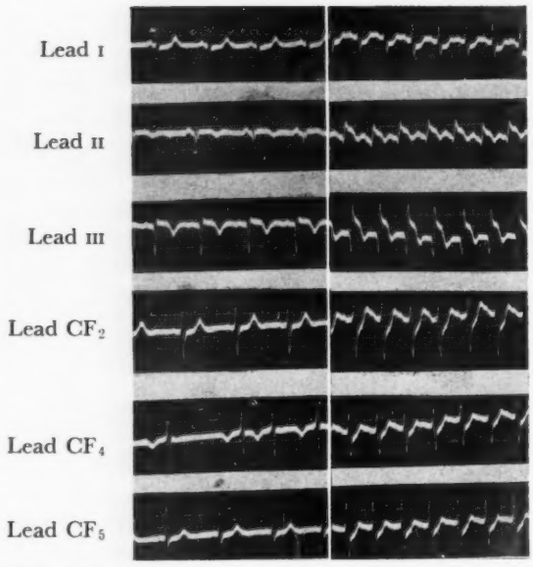


FIG. 4. Case III. Electrocardiograms before and after rupture of posterior papillary muscle (May 4 and May 7, 1948).

bile ducts appeared normal. Microscopic studies were not available.

The anatomic diagnosis was as follows: (1) acute suppurative cholecystitis with rupture of the gallbladder; (2) adjacent abscess of the liver; (3) bronchial pneumonia (both lower lobes); (4) infarct, anterior wall of the left ventricle and (5) rupture of the papillary muscle.

CASE III. B. E. L., a married woman aged sixty-one, suffered severe substernal pain with development of shock on May 4, 1948. She did not have any previous history of heart trouble or of hypertension although she had had attacks of what was termed acute indigestion. On admission the patient was cold and perspiring. Her blood pressure was 136 systolic and 84 diastolic and the pulse rate 100. Neither murmur nor rub was heard. An electrocardiogram showed a typical pattern of posterior myocardial infarction. (Fig. 4.) The circulation time (arm to tongue using macasol) was forty-five seconds. The venous pressure was 22 cm. of water.

On May 7th at 4:45 A.M. the patient was found by her nurse sitting on the side of the bed in severe pain. She had an involuntary bowel movement, became "wild and irrational" and tossed about the bed. The skin was cold and perspiring. The pulse could not be felt, the heart sounds were faint but audible and a gallop rhythm was present. At 6:00 A.M. pulmonary edema appeared. The heart rate was

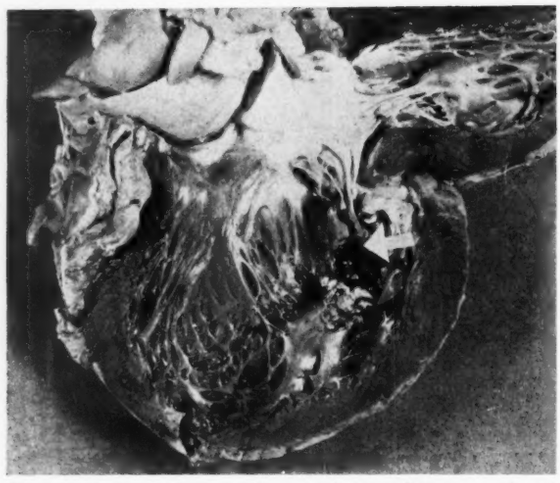


FIG. 5. Case III. Ruptured posterior papillary muscle of the left ventricle.

140. (Fig. 4.) At 8:45 A.M. a faint rub, interpreted as a pericardial rub, was heard at the pulmonic area. The sounds were faint and no murmur was heard. The blood pressure was unobtainable. The patient became cyanotic and died at 9:35 A.M.

Necropsy disclosed rupture of the posterior papillary muscle of the left ventricle 1 cm. below the attachment of the chordae tendineae. (Fig. 5.) Section through both ends of the broken muscle revealed complete infarction. There was infarction of the entire posterior half of the left ventricle and a large thrombus occupied 5 cm. of the ruptured coronary artery beginning 4 cm. beyond the origin of the vessel. The left coronary artery showed grade 2 sclerosis with narrowing but no thrombosis.

CASE IV. H. A. H., a man aged sixty, was seen on April 16, 1935. For two weeks he had had severe substernal pain after walking. His pulse, temperature and respirations were normal. Abnormal findings in the heart and lungs were not found. There was moderate tenderness in the epigastrium, with slight rigidity. No masses or jaundice was noted. On April 21st a hospital note read, "Patient came on ward breathing with the greatest difficulty, somewhat irrational, very restless, and with skin feeling cold and clammy." A later note: "Blood pressure too low to be taken. Heart sounds hidden by the effort of breathing. Hepatic margin well below costal margin. Pitting edema shows in legs to above knees. Ascites questionable. Patient expired."

At necropsy on April 22, 1935, the following was revealed: "Heart was greatly dilated. The coronary arteries were sclerotic and stenosed,

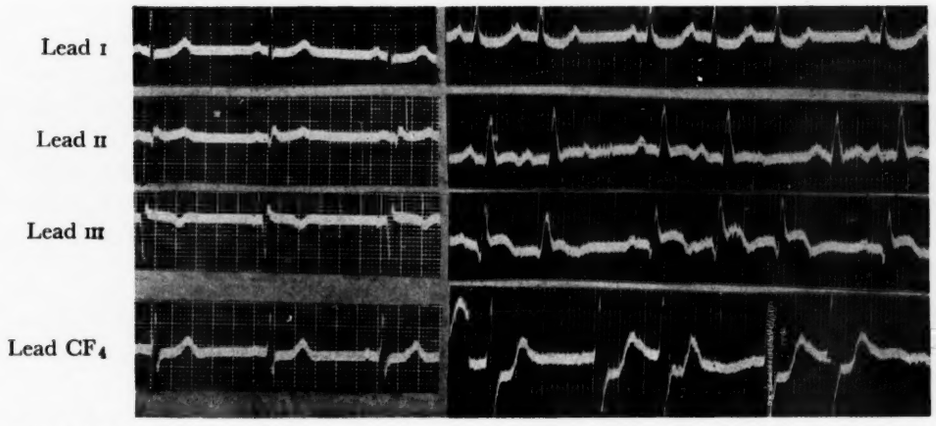
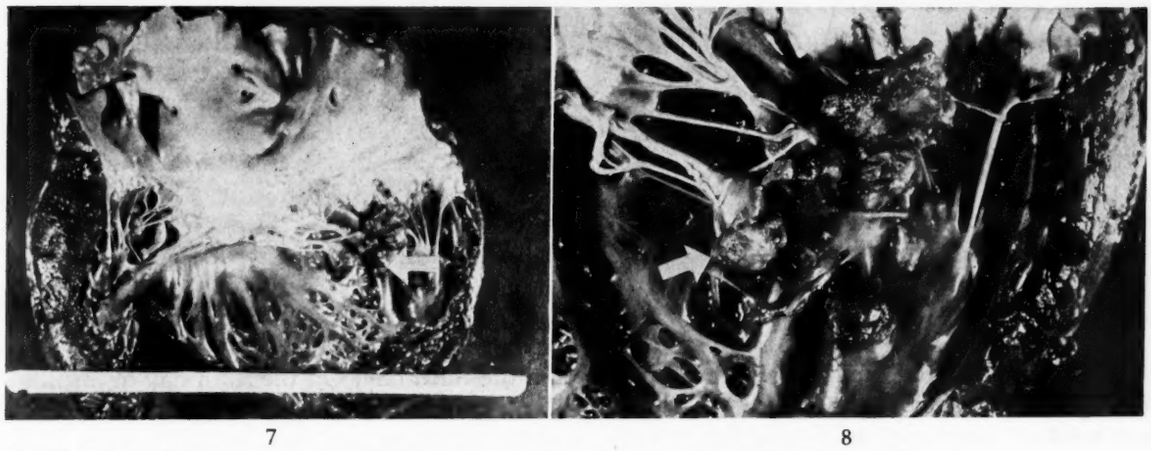


FIG. 6. Case V. Electrocardiograms before and after rupture of posterior papillary muscle (July 8 and July 16, 1948).



7 8

FIG. 7. Case V. Necrosis, rupture and disappearance of portion of posterior papillary muscle.
FIG. 8. Case V. Posterior papillary muscle ruptured with free, dangling portion of muscle attached to chordae tendineae; thrombus attached to chordae tendineae.

grade 4, with massive infarction of the left ventricle and sloughing of one of the papillary muscles to the mitral valve, resulting in complete incompetency of the said valve."

CASE V. E. L., a man aged sixty, on July 7, 1948, suffered a severe constricting substernal pain, perspired freely and felt weak and moderately short of breath. An electrocardiogram was taken the following day. (Fig. 6.) The patient was admitted to Huntington Memorial Hospital in Pasadena July 9th. During the following nine days the patient was fairly comfortable with nearly complete cessation of pain.

At 4:20 P.M. on July 16th the blood pressure was 128 systolic and 64 diastolic. A note said, "Patient seems better." The cardiac rhythm was regular except for not infrequent premature beats; the sounds were slightly distant, of fair quality. No murmur or friction rub was heard. At 5:00 P.M. he had sudden, severe substernal pain associated with grayish cyanosis and cold perspiration. Examination revealed a gallop rhythm and premature beats. The rate was 100, respirations 20 and the blood pressure 104 systolic and 70 diastolic. A "loud, high-pitched pericardial friction rub" was heard over the apex and above the left sternal border at the fifth interspace. Marked edema soon developed; the patient became semi-comatose during the night and at 8:00 A.M. the following day the diffuse moist rales in the chest obscured the cardiac sounds. Death occurred seventeen and a half hours after the sudden collapse.

At necropsy the heart was moderately enlarged and weighed 410 gm. A large posterior infarct was present beginning at the extreme base and extending all the way to the apex. There was complete necrosis of the posterior papillary muscle and rupture had occurred in the middle. (Figs. 7 and 8.) A layer of gray fibrin was adherent to the surfaces of the ruptured muscle and a thrombus was attached

FIG. 9. Case VI. Rupture of posterior papillary muscle with twisted, tangled chordae tendineae.

to the chordae tendineae of this muscle. Infarction of the posterior portion of the septum in the basal portion of the heart was found in an area 3 cm. across but the distal part was not involved. There was marked coronary sclerosis with marked calcification and narrowing noted in all of the major trunks; in the first portion of the right coronary artery in a segment 1 cm. in length a recent thrombus was present. A thrombus, microscopically apparently the same age, was found in the first part of the left circumflex artery.

CASE VI. D. H., a married woman aged seventy-four, suffered mild epigastric pain June 28, 1947. When seen at home she gave a past medical history of mild hypertension for two years. The blood pressure was 180 systolic and 70 diastolic; the heart sounds were good. There was a soft systolic murmur at the apex. She was advised to stay in bed but continued to be moderately active. On July 10th the patient took two enemas and two hours later became nauseated and vomited. She was seen at home and by that time diffuse pulmonary edema had developed. The blood pressure was 80 systolic and 50 diastolic. The "heart had one loud, rough, blowing murmur that blotted out any normally sounding heart sounds." She was sent by ambulance to the Huntington Memorial Hospital in Pasadena where she died soon after arrival.

At necropsy the heart weighed only 280 gm. A large recent posterior infarct measuring fully 3.5 cm. broad was present extending from the base down through the apex and there was involvement of the posterior portion of the septum for a distance of 1.5 cm. The infarction involved largely the subendocardial part of the muscle and some non-necrotic muscle was present under the epicardium. Complete rupture of one posterior papillary muscle was present about in its middle. The fractured surfaces were quite irregular, dull gray and soft. The rest of the muscle was intact and there were not any noteworthy valvular lesions. (Fig. 9.) High grade coronary sclerosis with marked fatty and fibrous plaque formation was found narrowing the lumina of all of the major trunks markedly, including the right coronary artery which supplied the area of necrosis. Although this area was taken out in one piece and sectioned at various levels, no thrombus was seen grossly or microscopically.

CASE VII. (Courtesy of Dr. Francis C. Wood and Dr. Thomas M. Kain, Jr.) "Mr. R. L. was seen with Dr. Thomas M. Kain on January 10, 1947. He was a man of 64 who had had hypertension but who was otherwise well until seven weeks previous to the night I saw him. While carrying a heavy roll of paper he had a sudden severe pain in both arms and across his chest anteriorly and he became slightly nauseated. He was able to finish his day's work, but with difficulty; when he arrived home at 5:00 P.M. he collapsed. His blood pressure, which had been 180 systolic and 100 diastolic in the past, dropped to 90 systolic and 60 diastolic. He had fever for ten days. He coughed up some blood on the third day. On the sixth day of his illness Dr. Kain noted a rough systolic murmur at the apex and over the lower part of the left precordium which had not been there before. His electrocardiogram showed fairly definite evidence of recent posterior cardiac infarction. He then got along quite well for about five weeks; then auricular fibrillation developed. The attack stopped after some quinidine was given. Auricular fibrillation began again on January 9, the day before I saw him. When I examined him his blood pressure was 110 systolic and 75 diastolic, the heart was rapid and irregular—130 per minute—and there was slight cyanosis. Dullness and distant breath sounds were heard at the right base; the veins and the liver were not engorged, and there was no edema. He lay quite comfortably flat in bed without respiratory difficulty, but he had had a good deal of hacking cough in the last two days."

Dr. Wood wrote to Dr. Kain on January 13th as follows: "Auscultation of his heart showed a musical, fairly high pitched systolic murmur all over the lower precordium. It was loudest just below the nipple, and died out in all directions from that point. My diagnosis of this patient is a probable coronary occlusion seven weeks ago.

FIG. 10. Case VII. Ruptured posterior papillary muscle.

FIG. 11. Case VIII. Ruptured anterior papillary muscle, showing rounded, smooth, healed end of muscle.

The murmur might be due to dilatation of the left ventricle, or to rupture of one of the papillary muscles. It does not sound like a perforated interventricular septum. Moreover, the absence of venous and hepatic congestion are unusual in a perforated interventricular septum."

The patient was seen again on January 21st in cardiac failure with a very rapid ventricular rate (about 180) and auricular fibrillation. He was cyanotic, with diffuse rales in his lungs and spitting of blood. The veins were engorged. The liver was down 4 fingerbreadths. There was no peripheral edema. He had some fever and a leukocyte count of 25,000. The blood pressure was 140 systolic and 90 diastolic.

Dr. Wood made a note at this time: "All these findings point to the fact that he had a coronary occlusion, possibly with a rupture of one of his papillary muscles."

The patient died a few days later and his heart showed rupture of the posterior papillary muscle. (Fig. 10.)

CASE VIII. (Courtesy of Dr. Francis C. Wood and Dr. William A. Jeffers.) Dr. Wood wrote, "The second case I saw was that of Dr. G. D., aged 70 at death. He had had angina of effort since 1938 and had an attack in August 1941 when we diagnosed a small cardiac infarct. He was admitted to the hospital seven years later (April 25, 1948), under the care of Dr. William A. Jeffers, after a severe prolonged attack of substernal pain which looked like another coronary occlusion. His blood pressure was 220 systolic and 120 diastolic on admission. His heart was enlarged. The next day his blood pressure dropped to 100 systolic and 80 diastolic, and a loud murmur developed at the apex. He went into cardiac failure. He had minor grade heart block. He had a pulmonary infarct, but he made a partial recovery and went home from June 13 to July 7, on which date he came back in congestive failure and paroxysmal dyspnea; he died October 15. Necropsy revealed rupture of a papillary muscle."

At necropsy the heart weighed 600 gm. The myocardium of the posterior wall of the left ventricle and adjacent portion of the septum was thin, firm and contained streaks of dense fibrous tissue. A second small myocardial scar was located in the lateral wall of the left ventricle. The anterior papillary muscle was separated at a point 2 to 3 mm. from its origin, the free border being rounded, smooth and apparently covered by endocardium. (Fig. 11.) There was generalized severe arteriosclerosis of both coronary arteries. A portion of the right coronary artery appeared to have been recanalized but there was not any evidence of a recent thrombus.

Comment. Apparently rupture occurred April 26, 1948. Although congestive failure ensued, the patient lived nearly six months. At necropsy the papillary muscle showed a smooth endothelialized end indicating healing. Rupture, therefore, does not necessarily cause death quickly and is compatible in certain instances with survival for a few months.

ELECTROCARDIOGRAPHIC CHANGES

The electrocardiographic changes following rupture of a papillary muscle have consisted of either exaggeration of the original pattern of myocardial infarction or no particular change except sinus tachycardia. Davison[1] had tracings in two of his three cases which merely evidenced infarction of

the posterior wall. Wood mentioned minor grade heart block in one instance. In Case VII the pattern was that of posterior myocardial infarction.

In one of our cases (Case V) partial auriculoventricular block with Wenckebach periods was found. (Fig. 6.) Lowry and Burn[5] observed first degree auriculoventricular block associated with T_3 type of myocardial infarction. In both Case III and Case V of our series the ST changes of posterior wall infarction were exaggerated.

COMMENTS

The recording of thirty-seven instances of rupture of a papillary muscle in relation to approximately sixty instances of rupture of the interventricular septum suggests that it should be considered as a complication of cardiac infarction when a loud murmur suddenly appears. Its observance twice in less than a year in the necropsy services of two private hospitals is of interest from the standpoint of mathematical probability (Cases I and III and Cases V and VI). Dr. Wood observed his two cases in less than two years.

Are there any criteria by which an antemortem diagnosis of ruptured papillary muscle may reasonably be made? A review of the thirty-seven cases of spontaneous rupture suggests certain helpful tentative clinical criteria.

A precise diagnosis of the lesion is difficult. Even in the earlier recorded cases, however, doctors and patients have suspected that some tissue had ruptured in the heart. In 1811 the brilliant French clinician Corvisart[9] surmised there had been a tearing in some part of the heart of the patient he described. In another instance the patient himself, as described by Wankel,[12] believed that something had torn in his heart and a diagnosis of acute mitral insufficiency of undetermined origin was made by Wankel. A sudden, loud precordial systolic murmur in the presence of myocardial infarction usually suggests rupture of the interventricular septum but it apparently also should suggest the possibility of rupture of a papillary muscle.

It is interesting that an incorrect diagnosis of ruptured papillary muscle led to the recognition of the syndrome of rupture of the interventricular septum. Brunn[13] in 1923 diagnosed endocarditis with rupture of a papillary muscle in a patient in whom a long systolic murmur with a rough systolic thrill developed following severe substernal pain. Necropsy revealed a septal rupture with thrombosis of the left anterior descending coronary artery. Later, in another patient with severe pain in the chest and shock, a rough systolic murmur and a fine systolic thrill developed. The diagnosis then made was that of septal perforation in view of his former experience. At necropsy such a perforation was found. This was the first recorded case in which an antemortem diagnosis of septal perforation following myocardial infarction was made and proved. The differential diagnosis from ruptured papillary muscle still presents a problem. This differentiation will depend largely upon positive physical findings.

Before the diagnosis of either rupture of a papillary muscle or of the interventricular septum can logically be considered, a murmur should either appear suddenly or a previous murmur should suddenly increase in intensity. In only ten instances of ruptured papillary muscle (four in this report) was this relationship established.[1,6,14] Although murmurs were observed in twenty-two instances, in the other cases examination prior to the rupture was not recorded.

The rupture in four instances (two in this report) was reflected by the appearance of an apparent friction rub.[5,15] This finding can be of only limited help in the diagnosis of a ruptured papillary muscle as it more often may indicate a new myocardial infarction or an extension of the original infarction.

Dr. A. G. Foord* pointed out a probably significant time relationship between the onset of the rupture and the onset of the apparent rub. Whereas following myocardial infarction the rub does not usually

* In clinicopathologic conference discussion of Case V.

appear for two or three days, in Case III and in Case V the friction rub was heard very soon after the apparent time of rupture.

The mimicry of a friction rub by the intracardiac lesion was quite convincing to the examiners. Although all the criteria for the diagnosis of a pericardial rub were not present, the rough quality of the sound was considered as quite characteristic of a friction rub; yet in no instance in which such a sound was heard was there associated pericarditis demonstrated at necropsy.

The explanation for production of the vibrations producing the sound was thought by Lowry and Burn[5] to be motion of the twisted chordae tendineae. In Case III and in Case V of our series, however, the remnant of the muscle was not tangled in the strands and in each a pseudorub was heard. Mimicry of a friction rub by certain murmurs is well known. Rupture of a papillary muscle is apparently an intracardiac lesion prone at times to give rise to sounds which are indistinguishable by auscultation from the friction rub produced by pericarditis.

A puzzling feature is the inconstant and relatively infrequent finding of a loud murmur in rupture of a papillary muscle. In many instances murmurs are not mentioned. Whereas a murmur is heard in about 96 per cent of patients with ruptured interventricular septum, it has been recorded in less than half of the patients with ruptured papillary muscle. This might be explained in some instances by the suddenness of death or as faulty observation; however, in several patients who were carefully examined before death significant murmurs were not heard. In Cases I and III (personally observed) although careful auscultation was practiced in each, in one a loud, harsh, diffuse precordial murmur was heard and in the other only a faint sound interpreted as a rub was audible. There was a similar drop in blood pressure in each, so the acute hypotension cannot adequately explain the difference in intensity. Davison[1] analyzed thirty-one cases and found abnormal heart sounds recorded in nineteen instances. In thirteen, apical systolic murmurs were heard; four of these were associated with diastolic murmurs. In one instance a systolic basal murmur was heard and once a diastolic murmur alone was heard at the apex. Among our eight cases a loud, rough-blowing systolic murmur (grade 4 plus) was heard all over the precordium in two instances; in two the loud murmur was chiefly apical; a pseudorub was heard in two instances while murmurs were not noted in the remaining two cases. In another found in the literature[7] a murmur was not mentioned.

TABLE I

MURMURS AND THRILLS OCCURRING IN REPORTED INSTANCES OF RUPTURED INTERVENTRICULAR SEPTUM AND RUPTURED PAPILLARY MUSCLE

	No. of Cases	Systolic Murmur	Per cent	Diastolic Murmur	No. with Thrills
Ruptured interventricular septum..	47	45	95.7	3	22
Ruptured papillary muscle.....	37	17	47.0	5	0

TABLE II

DIFFERENTIAL DIAGNOSTIC FINDINGS BETWEEN RUPTURE OF INTERVENTRICULAR SEPTUM AND RUPTURE OF A PAPILLARY MUSCLE

	Murmur	Thrill	Pseudo-rub	Clinical
Rupture of interventricular septum	Present in 96%; maximal intensity at left border of sternum; nearly always systolic	Present in over 50%	Never heard	Onset not necessarily abrupt; death may be postponed; right ventricular failure
Rupture of papillary muscle	Present in less than half; maximal intensity at apex or is first apical; may be systolic or diastolic	Never found	Heard occasionally	Onset usually abrupt; death usually soon,* hours or days; left ventricular failure

* Two exceptions: Cases VII and VIII.

Quite in contrast is the high incidence of auscultatory findings in interventricular rupture. Forty-five of forty-seven patients with interventricular rupture after myocardial infarction had systolic murmurs.[16] (Table I.) In two instances murmurs were not audible. Twenty-two of the forty-five with systolic murmurs had a systolic thrill. In the event a loud murmur does appear certain points may prove of diagnostic value

in differentiating ruptured papillary muscle from ruptured interventricular septum.

What are the Significant Points in the Differential Diagnosis? Ruptured chordae tendineae can cause a harsh systolic murmur and a thrill. This lesion has been reported in *however, was the absence of a thrill in every instance of ruptured papillary muscle.* This differential point would seem important. Although over 50 per cent of the patients reported with murmurs after ruptured interventricular septum had thrills, in none of

TABLE III

SUMMARY OF FINDINGS IN EIGHT PATIENTS WITH SPONTANEOUS RUPTURE OF A PAPILLARY MUSCLE OF THE HEART

Case	Etiology of Associated Condition	Muscle Involved	Murmurs	Necropsy Findings	Clinical Course	Comments
I	Periarteritis nodosa	Anterior	Loud systolic	Periarteritis of heart, liver and bladder; rupture of anterior papillary muscle*	Died in 24 hr.; pain, collapse, pulmonary edema	Diagnosed as possible valve rupture; clinical picture: sepsis
II	Sepsis; myocardial infarction	Anterior	No murmurs	Myocardial infarction; rupture of anterior papillary muscle*	Died in 4 da.; shock, pulmonary edema	Chills, fever, sepsis from ruptured gallbladder preceded rupture of papillary muscle
III	Myocardial infarction	Posterior	No recognizable murmurs (rub)	Rupture of posterior papillary muscle	Died within 51 hr.; pain, collapse	"Rub" heard soon after attack; possible rupture suspected but not particular site
IV	Myocardial infarction	Not stated	No murmurs	"Infarction of left ventricle"; ruptured papillary muscle	Died in 24 hr.; congestive failure, collapse	Diagnosis not suspected
V	Myocardial infarction	Posterior	No murmur (rub)	Posterior septal myocardial infarction; rupture of posterior papillary muscle	Died in 17 hr.; pain, collapse	"Loud, high-pitched pericardial rub" immediately after rupture
VI	Myocardial infarction	Posterior	Loud systolic	Posterior myocardial infarction; no coronary thrombosis; rupture of posterior papillary muscle*	Died in few hr.	Diagnosis not suspected
VII	Myocardial infarction	Posterior	Musical systolic murmur; auricular fibrillation	Ruptured posterior papillary muscle	Died after 8 wk.	Correct antemortem diagnosis
VIII	Myocardial infarction	Anterior	Loud apical systolic	Old posterior myocardial infarction; healed rupture of anterior papillary muscle	Lived 6 mo.	Correct antemortem diagnosis

* Torn end caught between twisted chordae tendineae.

long-standing heart disease other than myocardial infarction[17] and in endocarditis, but we could find no instances occurring as a result of myocardial infarction. It can be ignored, therefore, as a cause of a suddenly appearing murmur in myocardial infarction. The murmur is nearly always systolic if due to ruptured interventricular septum but may be both systolic and diastolic if due to rupture of a papillary muscle. An apparently significant differential point is the presence or absence of a thrill. Among forty-five cases of interventricular septal rupture collected by Fowler and Failey[16] in which physical findings were known, twenty-two of the forty-three patients with systolic murmurs had systolic thrills. *A remarkable finding,* the twenty-two patients with murmurs after a ruptured papillary muscle was the presence of a thrill mentioned after an attack. Dr. Wood's emphasis upon the difference between the location of the murmur arising from rupture of the papillary muscle and the murmur due to ruptured interventricular septum would seem important. In discussing the criteria for his diagnosis and answering a query as to whether or not thrills had been felt, Dr. Wood wrote to me, "The signs produced by a ruptured papillary muscle and a rupture of the interventricular septum seem to me to be definitely different especially with regard to the location of the murmur. In the 3 patients in whom I have diagnosed a rupture of the

interventricular septum the murmur has been loudest in the sternal area, and 2 of them had a thrill. In the 2 patients in whom I have diagnosed a rupture of a papillary muscle the murmur has been loudest in the vicinity of the cardiac apex, and I do not recall that either of them had a thrill, although I am not absolutely certain."

Another differentiating point is the type of immediate reaction in the two conditions. Sudden collapse is not necessarily a sequel of ruptured interventricular septum, and death may not occur for days, weeks, months or even years.[18] Rupture of a papillary muscle on the other hand is usually immediately followed by collapse. In many of the recorded cases collapse and sudden death occurred even before the diagnosis of myocardial infarction had been made. Death occurs usually within a matter of hours or a few days. (Tables II and III.)

Two notable exceptions are the two cases of Wood. One patient lived eight weeks and the other nearly six months after the rupture. Dr. Wood emphasizes another differentiating point: Venous and hepatic congestion are apt to follow rupture of the interventricular septum if the patient lives long enough, whereas after rupture of the papillary muscle in the left ventricle, pulmonary edema is the usual immediate sequel.

Although it is apparent that a diagnosis of ruptured papillary muscle must still be a presumptive one, it can be logically suspected in certain instances. If a murmur does not appear or if the adventitious sound is a pseudorub, the diagnosis can be only guessed at as one of the causes of the usual accompanying circulatory collapse. If a murmur does suddenly appear and an associated thrill is not felt, the diagnosis of rupture of the papillary muscle can be made if the murmur is chiefly apical and there is little subsequent venous congestion. Based upon the data available to the present it would seem, however, that if a thrill is associated with the murmur, a ruptured papillary muscle is unlikely. This is apparently a positive physical finding which differentiates ruptured interventricular septum and rupture of a papillary muscle.

In addition to its association with myocardial infarction, rupture of a papillary muscle must be considered as a possibility when a systolic apical murmur suddenly appears in association with endocarditis, sepsis and syphilis. It has been recorded once in the course of periarteritis nodosa.

SUMMARY

1. A review has been made of instances of ruptured papillary muscle of the heart.

2. Another case is added with a different etiology, that of periarteritis with necrosis of the muscle.

3. Tentative criteria based upon deductions from the data in thirty-seven cases are suggested for the antemortem diagnosis of ruptured papillary muscle.

4. "In a patient with cardiac infarction who suddenly collapses and in whom a loud systolic murmur develops at the apex without a thrill, if you think of and diagnose a ruptured papillary muscle, you will sometimes be right." (Wood)

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* Since this paper was written a report of two additional instances of spontaneous rupture of a papillary muscle of the heart following cardiac infarction has appeared. (Smith, J. C. Rupture of a papillary muscle of the heart; report of two cases. *Circulation*, 1: 766, 1950.) The correct diagnosis was made postmortem. The posterior papillary muscle was ruptured in both cases. A thrill was not felt in either instance.

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Seminars on Renal Physiology

Renal Excretion of Water, Sodium, Chloride, Potassium, Calcium and Magnesium*

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THE concepts and investigational technics of renal physiology which have proved so useful in elucidating the mechanisms by which various organic substances are excreted have not, to date, proven similarly effective in clarifying the processes by which the volume and electrolyte content of the body fluids are regulated. This is due, in part, to a difference in the nature of the information which is necessary for such an understanding. In many of the renal mechanisms which have been more or less adequately defined the functional role of the kidney has been either strictly excretory or adapted to conservation of the material concerned. In the case of sodium, potassium, chloride, bicarbonate and water the function of the kidneys is regulatory as well as excretory. Changes in excretion which are of insignificant proportions in the excretion of most other substances are the object of central interest in the renal control of water and the major electrolytes. Loss of 1 per cent of the glucose filtered at the glomeruli may be disregarded and tubular reabsorption under such circumstances considered to be "essentially complete." Loss of an extra 1 per cent of the filtered sodium in a normal individual would correspond to an excess excretion of about 15 gm. of salt per day, an amount which cannot be regarded as insignificant.

A satisfactory elucidation of the renal mechanisms for electrolyte excretion has lagged not only as a result of the necessity for taking into account small changes in rates of reabsorption and excretion, but also because of the complex interrelations involved between cations and anions, between different ions of similar charge and between water and electrolytes. A further difficulty is the multiplicity of factors involved in the control of the renal tubular transport of electrolytes and water.

This discussion cannot purport to be a review of this extensive and complex subject. It is intended largely to indicate the many unsolved and intricate problems and to present some of the background against which work in the field must be considered.

EXCRETION OF WATER

It has long been recognized that water is reabsorbed by two separate and dissimilar processes which have been termed "facultative" and "obligatory" reabsorption.[1] The need for such an interpretation arises from the observation that it is impossible, by the ingestion of water, to obtain a flow of urine which is more than 10 to 15 per cent of the total volume of fluid filtered.[1,2] A similar situation is observed in diabetes insipidus in which, even in the most severe cases, the urine flow does not begin to approach the rate of formation of glomerular filtrate.[3,4] It was suggested[1] that the obligatory reabsorption is related to the reabsorption of osmotically active solutes in the proximal tubule, while facultative reabsorption, under the influence of the pituitary antidiuretic hormone, is exerted only upon that portion of the filtered water which escapes the

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proximal tubule. This hypothesis has been supported by a number of experimental observations. The most direct evidence is derived from the work of Walker, Oliver and their associates[5] who, by an extension of the micropuncture technic of Richards and his co-workers,[6] studied the composition of fluid collected from individual nephrons of the rat and guinea pig kidneys. Figures 1 and 2 from this work[5] illustrate the data most pertinent to the present discussion. The relatively constant osmotic pressure in the face of a decreasing volume remaining in the tubule (indicated by the rising concentration of non-reabsorbed creatinine) implies that the reabsorption of water is proportional to the reabsorption of osmotically active solute of which sodium and its associated anions constitute all but a small fraction. Unlike the situation in the amphibian kidney where a relatively small part of the total electrolyte reabsorption occurs in this segment,[7] a major portion of the filtered fluid and electrolyte is apparently reabsorbed in the mammalian proximal tubule. Extrapolation of the observed rate of reabsorption to include the entire proximal segment would place the amount of fluid delivered to the distal tubule in the general order of magnitude of that which may be excreted in water diuresis.

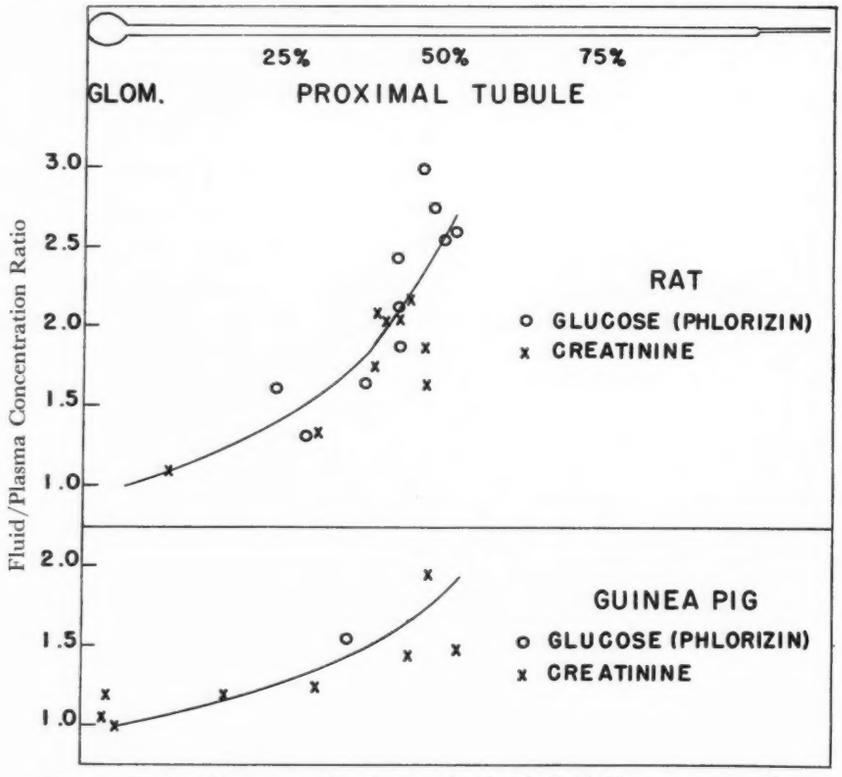

FIG. 1. Ratio of concentration in proximal tubule fluid to concentration in plasma for glucose (in phlorizinized animals) and for creatinine; approximate position of collection indicated by schematic proximal tubule at top. (Modified from WALKER, BOTT, OLIVER and MACDOWELL. *Am. J. Physiol.*, 134: 562, 1941.)

The loop of Henle was long considered to be the site of concentration of the urine. The absence of the thin limb in reptiles and amphibians and their failure to form a hypertonic urine under the influence of antidiuretic hormone led to the hypothesis that the mechanism for forming a hypertonic urine was located in this tubular segment.[8] However, the low epithelial lining of this part of the nephron would not appear to be adapted to the establishment of a sharp osmotic gradient[9] and this, together with the considerable variation in the length of this segment among the nephrons of the

same kidney, has caused doubt to be cast upon this hypothesis.[10] That concentration of the urine is a function of a more distal segment is strongly supported by the finding of a slightly hypotonic urine in the first portion of the distal tubule at a time when

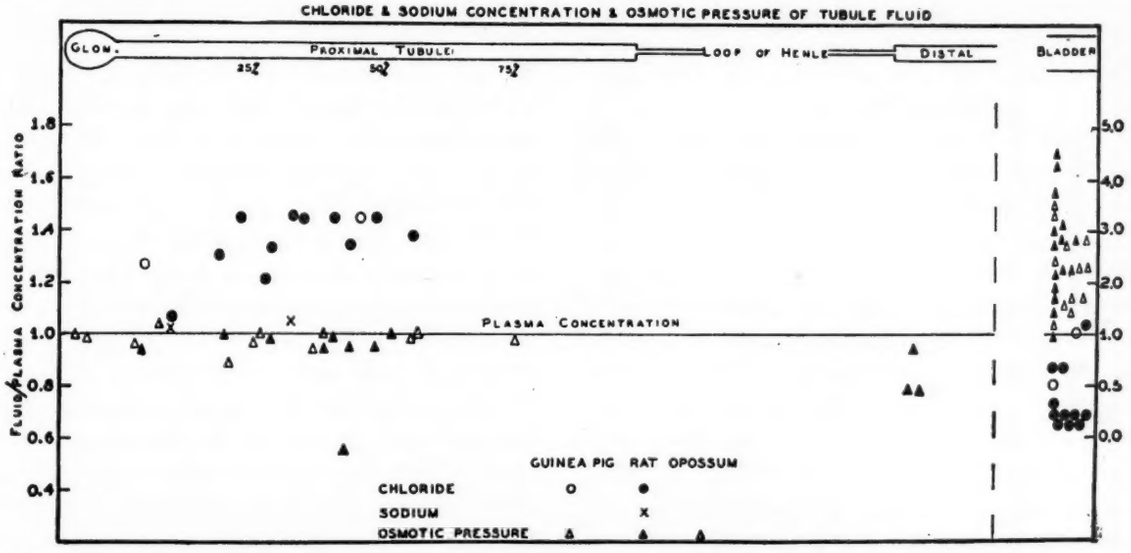

FIG. 2. Ratio of concentration of chloride and sodium and of osmotic pressure in tubule fluid and bladder urine to that in plasma. (From WALKER, BOTT, OLIVER and MACDOWELL. *Am. J. Physiol.*, 134: 562, 1941.)

the bladder urine was markedly hypertonic.[5] It has been proposed that the function of the loop of Henle is to permit the attainment of osmotic equilibrium by the passive back-diffusion of water following the reabsorption of most of the osmotically active solute in the proximal convoluted tubule.[11] The composition of the fluid delivered to the distal tubule has been the subject of considerable difference of opinion; all evidence presently available is entirely inferential. Although the urine halfway down the proximal tubule is isosmotic with the plasma,[5] there is no certainty that a similar situation exists when the end of this segment is reached. The various opinions concerning the tonicity of the fluid entering the distal tubule are bound up with opposing views on the site of sodium reabsorption. Shannon[12] proposed that the urine leaving the proximal tubule was markedly hypotonic as a result of failure of the diffusion of water to keep pace with reabsorption of almost all of the electrolyte in the proximal segment. Peters[13] has attributed reabsorption of a major fraction of the electrolyte to the loop of Henle. The slightly hypotonic urine in the first portion of the distal tubule[5] perhaps supports one or the other of these contentions; but since the volume of fluid remaining at that level was not determined, the magnitude of the electrolyte deficit is unknown. On the other hand, it has been assumed that the fluid escaping the proximal system has the same osmotic pressure as the plasma.[11] The experiments of Walker et al.[5] were done under anesthesia and frequently with osmotic diuresis, both of which may be presumed to have caused maximal antidiuretic hormone activity. No information is available, therefore, to indicate that the proximal tubule fluid is isotonic with plasma during water diuresis.

It is generally agreed that the volume of fluid reaching the distal segment is probably some 10 to 20 per cent of that filtered. Urine flows greater than this fraction of the glomerular filtration rate can be obtained only with osmotic diuresis which increases the outflow of the proximal system by reducing the reabsorption of both water and solute in that segment.[11,14–16] It has been proposed that under more normal circumstances a fixed fraction of the filtered fluid and electrolyte escapes the proximal tubule[11]

and that all or most of the water reaching the distal tubule is excreted in the absence of antidiuretic hormone activity.[9,11] Other observations indicate that the urine flow in maximum water diuresis varies with the rate of sodium excretion, when changes in the latter are, in part at least, independent of changes in glomerular filtration rate.[17] These findings are difficult to reconcile with the foregoing hypothesis.

There is a lack of unanimity concerning the factors which limit the degree to which the urine may be concentrated. When the rate of excretion of osmotically active materials is low, it would appear that the concentration of urine is limited by the attainment of an osmotic gradient against which further reabsorption of water is impossible.[1] There is some question as to whether or not all solute particles are equivalent in this regard. It has been stated that a higher osmotic pressure can be attained when urea is the major urinary constituent than when the urine contains large amounts of electrolyte and that maximum concentrations of urea can be superimposed on maximum concentrations of electrolyte in the same urine.[18–21] It has been pointed out[22,23] that some of the observations which led to these conclusions were made on rats allowed water ad libitum[26] so that there is no evidence that the urines were maximally concentrated. The results obtained are perhaps more indicative of the fact that ingestion of salt, presumably by drawing water from cells, produces thirst, while urea, which permeates cells more or less freely, does not lead to cellular dehydration and thirst.[22] The effect of increased excretion of osmotically active solute in the other studies may explain the lowered osmotic pressure when salts were administered since these were ingested in large amount. McCance and Young found an inverse relationship between urea and electrolyte concentration in the urine of dehydrated individuals[24,25] suggesting that the limit to the concentration of urine depends on total solute concentration and is independent of the nature of the dissolved substance. The results of Rapoport et al.,[26] although obtained on a number of different individuals and showing considerable scatter, are in general accord with those of McCance.

Maximally concentrated urine can be obtained only when the flow of urine is quite small, generally below 1–2 ml./min.[24–26] As the excretion of solute increases there is a change in the factors which set a limit upon the reabsorption of water. The maximum concentration attainable decreases as the urine flow rises so that in extreme osmotic diuresis no appreciable hypertonicity of the urine is detectable despite maximum antidiuretic hormone activity.[11,14,26] The nature of the limitation so produced is not certain. It has been attributed to a limited absolute capacity for facultative reabsorption of water similar to the Tm for glucose, etc.[11] Though in available experimental data no such absolute deficit in volume is detectable, uncertainty as to the volume and tonicity of the fluid delivered to the distal tubule for the action of this hypothetic mechanism makes interpretation difficult. It has also been proposed that there may be a limited capacity to perform osmotic work.[23] This concept likewise lacks quantitative experimental verification. The minimum urine flow is, however, fairly predictable from the rate of excretion of solute and is more or less independent of the identity of the substance excreted.[26] The nature of this relationship is indicated in Figure 3 from the paper of Rapoport et al.[26]

The capacity of the normal individual to form a highly concentrated urine is dependent on an intact supraoptico-hypophyseal system[4,27] and is presumed to be directly related to the concentration of circulating posterior pituitary antidiuretic hormone.[1,28,29] Extirpation of the pars nervosa of the pituitary, interruption of the supraoptic tracts or injury to the supraoptic nuclei lead to the production of diabetes insipidus. The latter procedures, which result in degeneration of the cells of the posterior pituitary where the antidiuretic hormone is believed to be synthesized and

stored,[4] are more reliable methods of producing diabetes insipidus presumably because there is less danger of injury to the anterior lobe of the pituitary, the integrity of which is essential for the production of permanent diabetes insipidus. Without antidiuretic hormone the renal tubule is unable to concentrate the urine normally[1,9] and the excretion of a large volume of dilute urine results. During dehydration, even in the absence of antidiuretic hormone, there remains some diminished capacity to form urine with an osmotic pressure distinctly greater than that of plasma.[12] This is presumably due to the fact that the volume of fluid delivered to the distal tubule for the action of the concentrating mechanism is markedly reduced as the result of a lowered rate of glomerular filtration.

The urine flow is ordinarily maintained at something below its maximal rate by the presence of antidiuretic hormone in the circulating blood. The rate of secretion of the hormone is believed to be under hypothalamic control[4,27] and normally varies in response to changes in the osmotic pressure of the body fluid[28,30,31] or, possibly more precisely, to changes in the state of cellular hydration. Decreases in the hydration of cells cause increased secretion of antidiuretic hormone; increases in hydration lead to diminished secretion. The receptor area sensitive to these changes in hydration is supplied by the internal carotid artery.[31] Apart from the state of hydration, increased secretion of antidiuretic hormone can be induced by exercise,[32] syncope,[33] emotional disturbance[34] or by a number of chemical agents;[35–38] diminished secretion is produced by chilling.[39] Graded changes in urine flow in response to administered antidiuretic hormone are obtained in the dog with diabetes insipidus only in the range of about 0.1 to 0.5 milliunits per hour[40] and this has been considered to be the physiologic rate of release of this substance. However, severe osmotic stimulation results in the appearance in jugular vein blood and excretion in the urine of considerably greater amounts.[41,42]

It is generally recognized that a normal response to the ingestion of water depends on more than an anatomically normal kidney and a normal supraoptico-hypophyseal system. Salt depletion[43] and other circumstances associated with abnormalities of the body fluids[44] are associated with impaired excretion of water. Several endocrines other than the posterior pituitary have effects on water excretion. Failure to develop permanent diabetes insipidus in the absence of the anterior pituitary[4,45–47] has already been referred to. The original hypothesis that the anterior pituitary elaborates a hormone which directly stimulates diuresis has generally been discarded in favor of the idea that the effect of the anterior pituitary is exerted through its trophic influence on one or more other organs. Pituitary growth hormone restores to normal the defect in renal function which follows loss of the anterior pituitary.[48] The effect of the thyroid on water excretion remains obscure. Although the disorder is not eliminated, the severity of diabetes insipidus may be diminished by thyroidectomy or increased by the administration of thyroid.[4] On the other hand, no clear abnormalities of water metabolism are induced by experimental hypo- or hyperthyroidism.

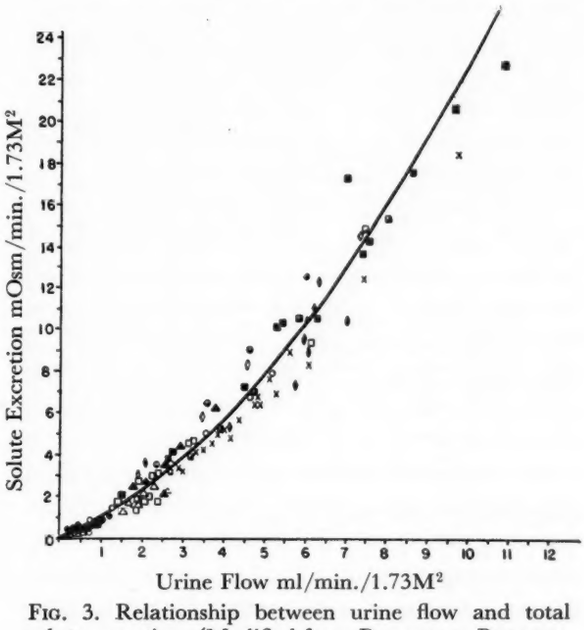

FIG. 3. Relationship between urine flow and total solute excretion. (Modified from RAPOPORT, BRODSKY, WEST and MACKLER. *Am. J. Physiol.*, 156: 433, 1949.)

The adrenal cortex has been especially implicated as essential for the occurrence of a normal water diuresis[49–51] and the abnormality of water excretion is the basis of a test for adrenal insufficiency.[52] The mechanism by which the adrenal steroids facilitate water excretion is not certain. Their effect appears to be exerted, in part at least, through their role in maintaining normal renal hemodynamics,[53–55] more particularly a normal rate of glomerular filtration, and probably through the maintenance of a normal volume and distribution of the body fluids. Evidence for the view that the adrenal cortical hormones exert an inhibitory effect on the tubular reabsorption of water (in direct antagonism to the pituitary antidiuretic hormone) and independently of their effects on electrolyte excretion has recently been reviewed by Gaunt et al.[56]

TABLE I

EXCRETION OF SODIUM DURING THE INFUSION OF ISOTONIC SODIUM CHLORIDE IN A DOG[61]

Period	Filtration Rate ml./min.	Plasma Sodium mEq./l.	Filtered Sodium μEq./min.	Excreted Sodium μEq./min.	Reabsorbed Sodium		
					Amount μEq./min.	Per cent of Filtered	Per 100 ml. of Filtrate mEq.
1	42.9	145.4	6250	9	6241	99.9	14.5
2	46.2	145.2	6700	12	6688	99.8	14.5
3	54.9	144.2	7930	71	7859	99.1	14.3
4	62.3	144.6	9000	208	8792	97.6	14.3
5	65.3	145.8	9520	351	9169	96.3	14.1
6	66.1	145.7	9630	487	9143	94.8	13.8

EXCRETION OF SODIUM AND CHLORIDE

The excretion of sodium and chloride may, with certain reservations, be considered as a unit. This is expedient since relatively few studies of renal electrolyte excretion have specifically dissociated the excretion of sodium from that of chloride. In many of the earlier studies of electrolyte excretion only chloride was measured, since the determination of sodium was considerably more difficult. Many of the phenomena noted were probably reflections of similar behavior of the sodium ion. More recently the flame-photometric determination of sodium has tended to relegate chloride to a place of lesser prominence. Chloride reabsorption has even been considered to be entirely non-specific and secondary to sodium reabsorption. This view would appear to be open to question since there are occasions when the body may be depleted of fixed cation by the necessity for excreting chloride, as when ammonium chloride is ingested[57,58] or when mercurial diuretics are administered to certain resistant patients.[59] In general, however, unless specific measures are taken to dissociate the two, the excretion of chloride roughly parallels that of sodium.

A few pitfalls to be avoided in the interpretation of data concerning the reabsorption and excretion of sodium may profitably be noted. Wesson et al.[11] have indicated the dangers inherent in quantifying the reabsorption of any substance in terms of the filtration rate when the amount of that material excreted is only a small fraction of the amount filtered, as is the case with sodium and chloride. The result of this mathematic operation is an approximation to the plasma concentration of the substance concerned. Another danger arises in considering a change in the ratio of filtered to excreted sodium to be an indication of altered tubular function;[60] such a change will occur simply as a result of variation in the amount filtered, so long as the increment in the amount reabsorbed does not exactly parallel the change in glomerular filtration. In addition, since the magnitude of changes in sodium excretion may be many times the range of variation in filtration rate, it is obvious that the amount excreted will be related to the fraction not reabsorbed rather than to the absolute amount filtered. However, the fraction not reabsorbed cannot be considered a function solely of tubular activity. Data obtained during the infusion of normal saline solution in a dog[61] may be used to illustrate these points. (Table I.) In this experiment there is an increase in the sodium filtered from 6,250 μEq./min. to 9,630 μEq./min., and in the sodium reabsorbed from 6,240 to 9,140 μEq./min. The excreted sodium increases

from 9 μEq./min. (0.1 per cent of the filtered) to 487 μEq./min. (5.2 per cent of the filtered). The percentage of the filtered excreted thus changes from 99.9 down to 94.8. The amount reabsorbed per 100 ml. of glomerular filtrate never differs much from 14.0 mEq./min. (the amount contained in the 100 ml. of glomerular filtrate). Depending on which aspect is considered, reabsorption might be interpreted as increased (absolute amount), unchanged (amount per unit volume of glomerular filtrate) or decreased (fraction of filtered). Certainly one is not in a position to say whether the change in sodium excretion is to be attributed to a change in filtration or tubular activity. Finally, a point that is frequently overlooked, the excretion of *any* anion requires the excretion of an equivalent amount of cation, and vice versa. The administration of an electrolyte, the anion of which can be reabsorbed only slightly or not at all or which is secreted by the renal tubules may carry with it into the urine a large amount of sodium although conditions may otherwise favor a very small excretion of sodium. This is the basis of several procedures designed to deplete the body of sodium, such as the administration of ammonium chloride[57] or ammonium thiosulfate.[62] When sodium thiosulfate or sodium p-aminohippurate is administered, excretion of relatively large amounts of sodium must be anticipated although the net sodium balance may be positive. While it is true that the cation excretion may be variably distributed between sodium and potassium under such circumstances, and useful information may sometimes be obtained from this cation pattern,[59,62,63] the excretion of sodium is related to the non-reabsorbed anion and not to any depression of the capacity of the tubules to reabsorb sodium.

One of the major problems to be dealt with in any consideration of the tubular reabsorption of sodium concerns the number of separate mechanisms involved. In addition to sodium reabsorption, which results in a net decrease in the electrolyte content of the tubular fluid (that is, reabsorption of both cation and anion), it is recognized[64,65,59] that sodium may be reabsorbed by what appears to be cation exchange for H^+, NH_4^+ or K^+. The question may be raised as to whether these disparate results necessarily indicate that fundamentally different processes are involved as far as the reabsorption of the sodium ion is itself concerned. The formation of intermediate compounds within the tubule cells in the transport of most organic substances[66] and even phosphate or sulfate[67] is a plausible concept but it is difficult to imagine Na^+, K^+ or Cl^- ions taking part in similar reactions. It has been proposed[68] that a cation exchange process accounts for all sodium reabsorption. While a system for cation exchange alone will not adequately explain the reabsorption of chloride, a co-existing anion exchanger might be expected to yield a system whose performance would correspond to observed phenomena. Exchange of hydrogen ions for sodium ions, in the absence of a system for anion reabsorption, would yield acidification and secretion of ammonia, as proposed by Pitts.[65] While experimental evidence for such a mechanism is yet to be obtained, it is a tenable hypothesis that sodium may be reabsorbed by a single tubular ion exchange process, the effects of which may, however, be modified by the presence or absence of other specific mechanisms in the several tubular segments. Dr. Pitts[69] has discussed those mechanisms for sodium reabsorption which result in acidification of the urine (and reabsorption of bicarbonate). Further discussion of sodium reabsorption in this paper will refer specifically to that which is accompanied by removal of fixed anion from the tubular fluid.

The amount of sodium excreted in the urine is rarely more than a very small fraction of that which passes the glomerular membrane so that the rate at which sodium is reabsorbed must very closely parallel the rate at which it is filtered. It has been proposed that the variation in reabsorption with filtered load is a characteristic of sodium transport in the proximal tubule

only, this segment operating in such a way as to permit delivery to the distal tubule of a relatively constant fraction of the filtered sodium.[11] Since, despite some interpretations to the contrary,[70,71] the preponderance of evidence favors the view that all the glomeruli in the normal mammalian kidney are continuously active,[72–76] and since the plasma sodium concentration is generally maintained within a very narrow range by corresponding adjustments of water excretion, it follows that the amount of sodium presented to the tubules for reabsorption depends largely on the volume of fluid filtered in each glomerulus. Changes in filtered sodium will then be reflected within the tubule largely by changes in the rate of flow of fluid through its lumen. It is difficult to conceive a mechanism which could operate under these conditions so that a constant fraction of the filtered would escape reabsorption. It seems more reasonable to accept the view, for which some evidence can be presented,[12,14,77] that the fraction of filtered sodium reabsorbed in the proximal tubule tends to increase with decreasing filtration rate. It would follow from either alternative that, other influences remaining constant, changes in filtration rate will be accompanied by proportionately larger changes in sodium excretion.

Since changes in sodium concentration were not found to occur with reabsorption in the proximal tubule,[5] some question remained as to whether an active tubular process was involved in electrolyte transport in this segment.* This has been answered in the affirmative by recent work on osmotic diuresis.[14,16,79] In this situation the osmotically active solute of the glomerular filtrate is not composed almost exclusively of sodium and its equivalence of anions, as it is ordinarily. As electrolyte is withdrawn and non-reabsorbable solute is not, the remaining solute contains a decreasing proportion of sodium. Since the total osmotic pressure of the fluid within the proximal tubule remains essentially that of plasma, the concentration of electrolyte must be reduced substantially below that of plasma. The effect of non-reabsorbed solute on the volume and sodium concentration of the tubular fluid is illustrated in Figure 4. The curves are based on the simplifying assumptions that the plasma osmotic pressure is made up entirely by sodium and its equivalent anions plus solute which cannot be reabsorbed by the renal tubules, and that the fluid in the tubule retains the same osmotic pressure as the plasma. The non-reabsorbable solute is calculated at 10 mOsm/L. in the "normal" situation, 100 mOsm/L. in osmotic diuresis. The development of a concentration gradient by a reduction of the concentration in the fluid below that of the plasma requires an active transport process. Reabsorption of sodium and chloride is also decreased under these conditions. This was attributed by Wesson and Anslow[79] to the development of a concentration gradient for sodium between proximal tubular fluid and plasma against which further transport of sodium is impossible. An hypothesis more easily explained in terms of the kinetics of the transporting mechanism would seem to be that of Mudge et al.[14] that the sodium concentration in the fluid within the tubule is probably an important factor in the rate at which this ion is transported and that diminishing reabsorption results from the falling sodium concentration which occurs. Neither of these hypotheses has taken into account the fact that, with diminished reabsorption of the contents of a tubular system of relatively fixed volume, the rate of flow in the more distal portions of the tubule must be greatly increased. Rapidity of flow may be an important factor in

* On the basis of the uptake of sodium and potassium by kidney tissue *in vitro*, Conway et al.[78] have concluded that no appreciable sodium reabsorption can be presumed to occur in the proximal tubule. It would seem hazardous to identify uptake from the medium with reabsorption from the tubular lumen as the authors have done. They challenge the view that a large fraction of the fluid is reabsorbed in the proximal tubule because the rate of collection of fluid in the experiments of Walker et al.[5] did not correspond to the presumed volumes remaining at different levels in various tubules. The weight of evidence from the concentrations of creatinine and glucose in the phloridzinized animal would seem to permit one to discount the latter criticism.

enhancing the amount of sodium which escapes absorption.

This interpretation of the effect of osmotic diuresis on sodium excretion has been challenged by Seldin and Tarail[80] because in their experiments less sodium was excreted in urea diuresis than when glucose or mannitol was the major urinary solute. However, the amount of osmotically active solute excreted in the experiments cited was considerably greater when mannitol and glucose were used than when urea was injected. Although factors other than the amount of non-reabsorbable solute can be shown to modify the amount of electrolyte excreted during osmotic diuresis,[14,16] the evidence that cellular dehydration is the predominant influence is inadequate.

The reabsorption of sodium and chloride assigned to the distal tubule by various investigators has varied considerably. In the amphibian most of the filtered electrolyte is reabsorbed in the distal tubule[7] but there is no *direct* evidence that any such mechanism is present in the mammalian distal segment. Wesson et al.[11] have postulated a fixed distal capacity to reabsorb sodium equivalent to about 12 per cent of the amount ordinarily filtered, basing their conclusions on the assumption of delivery to the distal tubule of a volume of isotonic fluid equal to that available for excretion in water diuresis. Duggan and Pitts[81] have found that the maximum effect of mercurial diuretics is to cause an increased excretion of sodium equivalent to about 20 per cent of that normally filtered. Assuming that these agents are capable of completely abolishing the mechanism on which their effect is exerted, the authors conclude that the capacity to reabsorb about 20 per cent of the sodium normally filtered resides in the distal tubule. Mudge et al.[14] have, however, found larger amounts of sodium excreted as a result of the injection of mercurials and infer from this and from the effect on potassium excretion[82] that the mercurial action on reabsorption is exerted

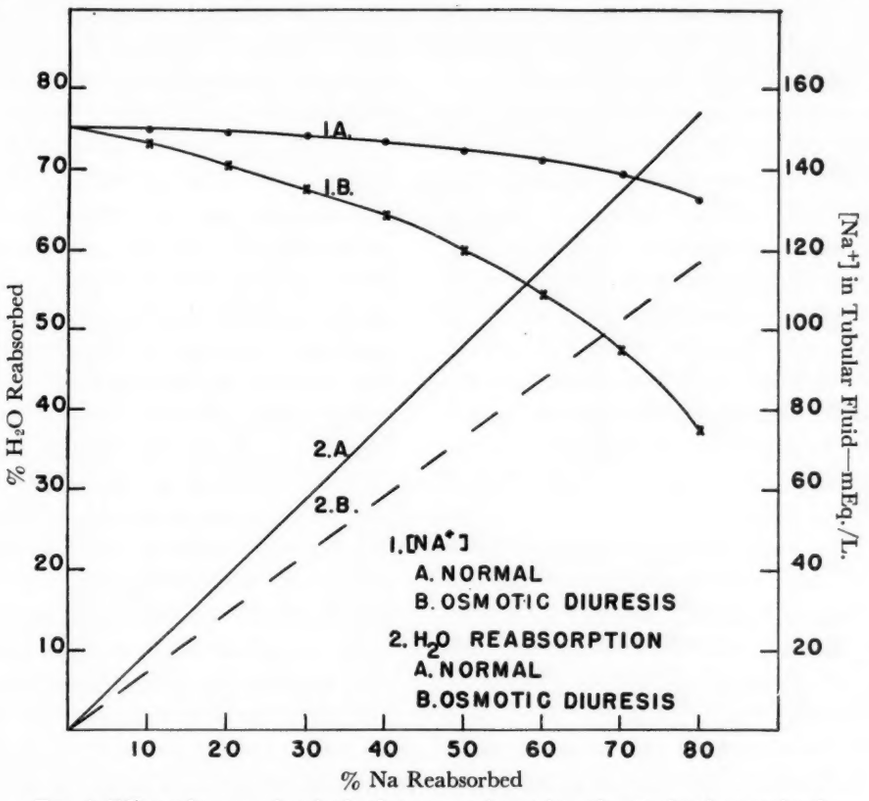

FIG. 4. Effect of non-reabsorbed solute on reabsorption of water by the proximal tubule and on the concentration of sodium in tubule fluid.

in the proximal tubule. It has been implied[12] that no appreciable reabsorption of sodium and chloride occurs in the distal tubule. No matter which of these views is accepted, it is apparent that the over-all reabsorption of sodium must be largely a reflection of that which occurs in the proximal tubule since the major fraction of the filtered sodium is reabsorbed in that segment.

The reabsorption of sodium is subject to modification by a number of extrarenal influences. The nature of some of these has been identified; quite probably others remain as yet unrecognized. The capacity to transport sodium is undoubtedly intrinsic to the cells of the renal tubules and it is probably only the rate of transport which is regulated by hormonal and other factors. Certainly, the isolated kidney of the heart-lung-kidney preparation continues to reabsorb a major fraction of the filtered sodium and chloride.[29]

Among the hormonal factors which regulate sodium excretion the best known are the adrenal cortical steroids. In the absence of the adrenal cortex the normal adjustment of sodium output to intake is not maintained[83,84] so that in the face of a normal or reduced intake this ion is lost in the urine. It is clear that this is a defect in tubular function, since it occurs despite a fall in glomerular filtration rate and the consequent decrease in filtered sodium.[85] Adequate balance may, however, be maintained by a marked increase in sodium intake.[86] This is one of the few instances in which the defect can be said to be cation-specific. There is some evidence that the adrenal steroids make possible not only the retention of sodium when intake is reduced, but also facilitate its rapid excretion when intake is high.[51,87,88] There are data to indicate that some of the steroid sex hormones, particularly progesterone, may also exert mild sodium-retaining effects.[89]

The antidiuretic hormone of the posterior pituitary can, under certain conditions, be shown to exert an inhibitory effect on sodium (or chloride) reabsorption.[40,88,90–92] The increase in electrolyte excretion following large doses of posterior pituitary preparations has been attributed to the oxytocic factor[90] but the "chloruretic" effect can be observed with doses of pitressin small enough to eliminate the oxytocic factor as an important contributor to the phenomenon.[40,91,92] There is morever some question as to whether the pressor (antidiuretic) and oxytocic principles are actually secreted as physiologically separate entities.[93,94]

In animals with one kidney denervated, more water and electrolyte is excreted on the denervated side.[95,96] The contribution of change in glomerular filtration to this increased excretion cannot be fully evaluated but the augmented electrolyte loss is probably, in part at least, independent of the increase in filtered load.[96]

Elevation of the renal venous pressure has been shown to diminish sodium and chloride excretion even if the rate of glomerular filtration is not depressed.[97] No simple explanation of this mechanism in terms of local changes is immediately apparent; it would be of interest to determine whether the same result could be obtained in the denervated kidney.

While the above factors have been shown to influence the tubular reabsorption of sodium, the question remains whether there are not additional determinants of tubular activity. Some others, such as the state of hydration of the body cells[80] and the renal oxygen tension,[98,99] have been suggested but the evidence that they are involved in the regulation of sodium excretion is not yet adequate.

The problem of most general interest concerns the integration of the various factors which influence sodium excretion and an evaluation of their individual contributions to the regulation of sodium excretion under any set of circumstances. The large number of possible variables involved has, to date, precluded any satisfactory solution of this problem. Attempts have been made to analyze the role of altered filtration rate, as opposed to that of altered tubular activity, in changes in sodium excretion in various experimental

and clinical conditions.[11,60,100–104] The fundamental difficulty in any such study involves the question of how much change in the amount of sodium filtered is required to produce a given change in the amount excreted if all other contributing variables remain unchanged. The establishment of sufficiently controlled and reproducible conditions to permit an approach to this question is one of the most important problems in renal physiology. The importance of this information may be seen from a consideration of some of the possibilities. If any increase in the amount filtered were reflected by excretion of this increment in the urine, an increase in filtration rate of only 1 ml./min. would mean the excretion of about 12 additional gm. of salt in twenty-four hours. On the other hand, if the *fraction* of the filtered sodium excreted in the urine were to remain constant, a change of a few per cent in the filtered load would have a negligible effect on the amount excreted. It would appear that the true relationship is somewhere between these extremes. The postulate of Wesson et al.[11] requires that about one-eighth of any increment in filtered sodium be excreted in the urine; even on such a basis small changes in filtration rate may be reflected by large changes in excretion. The hypothesis that the fraction of filtered sodium escaping reabsorption in the proximal tubule varies in the same direction as the filtration rate does not yield so simple a relationship, since the effect of an alteration in filtration rate would depend on the level from which such a change was made. However, under most circumstances a small change in glomerular filtration would be reflected in a marked change in the amount of sodium excreted. The patterns produced by several of these alternatives are indicated in Table II. Until some definitive information is obtained to indicate at least the order of magnitude of the changes in excretion to be expected from a given change in filtration, analysis of the contribution of tubular vs. glomerular factors to any particular modification of sodium excretion is hardly possible.

Whatever may be the relationship between filtration and excretion when other factors remain constant, it is apparent that under ordinary conditions these other factors practically never remain constant and changes in them may be sufficient to counterbalance changes in glomerular filtration rate completely. As extreme examples may be cited the continued excretion of sodium despite large decreases in filtration rate in adrenal insufficiency[85] or a fall in sodium excretion despite a rise in glomerular filtration after the administration of ACTH to normal subjects.[63,105,106] While one may feel fairly certain that an acute fall in filtration rate of considerable magnitude would result in a very marked decrease in sodium excretion, there are mechanisms by which equilibrium can be re-established at the lower level. Methods for evaluating the activity of some of the extrarenal factors and for quantifying their effect on sodium transport are badly needed.

An additional problem concerns the mechanism by which the necessity for sodium excretion or retention is detected

TABLE II

AMOUNTS OF FILTERED AND EXCRETED SODIUM PREDICTED FROM VARIOUS HYPOTHETICAL RELATIONSHIPS BETWEEN AMOUNT FILTERED AND REABSORBED (PLASMA SODIUM CONSTANT AT 140 MEQ./L.)

Filtration Rate ml./min.	Filtered Sodium μEq./min.	Sodium Excreted in μEq./min. with Reabsorption: of Constant Amount	of Constant Fraction of Filtered	of Constant Fraction* Plus Constant Amount	of Changing† Fraction of Filtered
115	16,100	0	92	0	10
120	16,800	0	96	16	25
125	17,500	100	100	100	100
130	18,200	800	104	184	200
135	18,900	1500	108	268	500

* These are amounts predicted from the hypothesis of Wesson et al.[11] Excreted = Filtered − (0.88 Filtered + 2000).

† The figures in this column bear no formal relationship to the amount filtered.

Note: 100 μEq./min. is equivalent to 144 mEq./24 hr. or the equivalent of 8.4 gm. of NaCl/day.

and mediated so as to preserve so remarkably the constant volume and composition of the body fluids in the face of extreme variations in sodium intake. Since the concentration of sodium in the body fluids normally is maintained within a very narrow range not by the retention or excretion of electrolyte but by the retention or excretion of water, it would appear that the maintenance of sodium balance requires some receptor sensitive to changes in volume.[107] It has been suggested that the filtration rate is in some way related to expansion and contraction of the extracellular fluid volume[11] and that variation in filtration rate is the major determinant of sodium excretion. The latter may well be the case in the dog in which large and rapid changes in filtration rate are easily produced with isotonic saline solution but would appear to be much less important in man in whom the rate of glomerular filtration is a highly stable function. However, this concept implies an unidentified volume receptor since changes in the volume of circulating fluid can affect the filtration rate *directly* only in so far as changes in blood pressure are produced. An interesting hypothesis recently advanced[108] is that the changes is interstitial fluid volume within the cranium, where such changes would have more tangible effects than elsewhere in the body, are of major importance in the regulation of sodium excretion.

It may be pertinent at this point to digress briefly on the problem of the abnormality of sodium excretion in clinical states associated with the accumulation of edema, particularly cardiac failure. It is apparent that since the changes in electrolyte concentration of extracellular fluid are always relatively slight when compared with the changes in extracellular fluid volume, the accumulation of any appreciable volume of excess fluid in the form of edema can occur only if a similar excess of electrolytes is retained. It has thus been apparent from the time that the composition of edema fluid was determined that there must be a decrease in the excretion of sodium and chloride, relative to intake, in conditions associated with the accumulation of edema. Although the abnormality was originally considered to be in the excretion of chloride (presumably because it was the chloride that was measured), it was soon recognized that it was sodium specifically that was involved[109,110] since the chloride of ammonium or potassium chloride was excreted normally while the sodium of sodium bicarbonate was retained. Recent interest in the concept of so-called "forward failure," which supports the contention that sodium retention precedes the elevation of venous pressure,[111,112] has given new impetus to the study of sodium excretion in cardiac failure but the problem of altered electrolyte excretion remains, whatever theory of congestive failure is accepted. The question devolves not upon whether but why sodium excretion is impaired, and thus upon the contribution of each of many factors in the integrated regulation of sodium excretion.

Changes in renal blood flow and rate of glomerular filtration have been advanced as the chief cause of sodium retention in cardiac failure.[102,112] Attention may be centered on the filtration rate since the blood flow *per se* is not directly involved in sodium excretion. In most patients with cardiac decompensation the filtration rate is depressed[98,102,112,113] but some have been found in the normal range.[98,112,113] In those with low rates of glomerular filtration there may or may not be a rise when compensation is regained.[98,113,114] Since the glomerular filtration rate may not rise with restoration of compensation, it is clear that other adjustments may allow for normal excretion of sodium despite a lowered filtration rate.

Other factors which, by themselves, would tend to yield a decrease in sodium excretion have also been shown to be operative in cardiac decompensation. In some patients there is an increased excretion of substances which exert an inhibitory effect on sodium excretion similar to that of desoxycorticosterone acetate;[115] in some a decreased sweat sodium concentration has

been found.[116] These have not, however, been uniform findings. The renal venous pressure is also usually increased in cardiac failure.[117] Decreased renal oxygen tension has been advanced as a possible explanation of the sodium retention[98] but other investigators have found decreased oxygen tension to increase rather than to decrease sodium excretion.[99] It would thus seem hardly possible to establish any unitary explanation for the altered sodium excretion in congestive failure and analysis of any individual situation would appear to depend on the interpretation of quantitative data for which no adequate basis of information is yet available.

EXCRETION OF POTASSIUM

In considering the mechanism for potassium excretion an additional complication is encountered in the capacity of the renal tubules to secrete potassium from blood to urine as well as to reabsorb potassium from the tubular lumen.[118–121] The absence of evidence for the existence of any secretory mechanism for sodium, chloride or bicarbonate justifies the assumption that the difference between the amount filtered and excreted is equal to the amount reabsorbed. Measurement of the excreted and filtered potassium, however, still leaves two variables, reabsorbed and secreted potassium, which cannot be independently determined. There is no method, at present, of distinguishing the contribution of secretion to potassium excretion except under special circumstances and then only within wide limits of possible variation.[59,82] It must be recognized, however, that secretion may be contributing to potassium excretion even when, as is normally the case, the amount filtered exceeds that excreted by a considerable margin and, conversely, reabsorption may be continuing even though the excreted potassium is greater than the filtered. From the effect of mercurial diuretics on potassium excretion under various conditions[82] and from the pattern of ion excretion when potassium salts are infused,[59] the occurrence of simultaneous reabsorption and secretion has been inferred. Ordinarily, however, when a change in potassium excretion occurs it is not possible to say whether it is the result of altered tubular reabsorption or secretion.

During the excretion of certain foreign anions it is possible to demonstrate that potassium secretion is accomplished by a process which results in the replacement of filtered sodium by potassium.[59] Although no evidence is at hand to indicate whether or not any intermediate steps are involved, the most plausible explanation would appear to be direct exchange of one cation for the other. In more usual circumstances it is not possible without qualification to infer evidence of the substitution of potassium for sodium even when potassium secretion is evident, but the most reasonable assumption is that the mechanism is the same and that all potassium secretion is cation exchange of sodium for potassium. The reabsorption of potassium probably occurs in the proximal convoluted tubule, secretion in the distal.[59,82] No information is available on the nature of the reabsorptive process.

The capacity to both reabsorb and secrete potassium allows greater latitude in the excretion of potassium at any given plasma concentration than is the case with any other substance which has been studied, the potassium clearance varying from practically zero to values approaching twice the rate of glomerular filtration. Some question of the capacity to reduce potassium excretion to very low values has been raised and it was believed that urine containing potassium at a concentration less than that in the plasma could not be formed.[122,123] However, although depletion of the body potassium does not necessarily result in a low renal potassium output,[122,124] the kidney does have the capacity to limit the excretion of potassium to negligible amounts[125,126] and to produce a urine less concentrated than the plasma with respect to this cation.[125–128]

The factors by which potassium excretion is regulated cannot yet be identified with any certainty. The amount filtered at the

glomeruli[59,129] and the amount delivered to the kidney by the circulating blood[75] are poorly correlated with the rate of potassium excretion and are probably less important in determining the rate of excretion than tubular transport, which is the important variable. At least two endocrine organs are known to influence potassium excretion—the adrenal cortex and the neurohypophysis. The adrenal cortical steroids enhance the excretion of potassium[85,130] and diminish the excretion of sodium. The fact that these changes are in opposite directions might suggest that this effect is exerted by increasing the exchange of potassium for sodium ions. Two circumstances militate against although they do not exclude[59] such an interpretation: (1) following administration of desoxycorticosterone[92] or of ACTH[106] the rise in potassium excretion frequently precedes the fall in sodium excretion, and (2) the decrease in sodium excretion is usually of greater absolute magnitude than the change in potassium excretion.

Posterior pituitary antidiuretic hormone also produces an increase in the excretion of potassium.[92] In this case the change in sodium output is in the same direction and the question may be raised as to whether the effect here is not primarily upon anion (chloride) reabsorption.

Although these endocrine influences may be important in the delicate adjustment of potassium balance, other factors far outweigh them in the capacity to produce large modifications of potassium excretion. Thus the administration of massive doses of desoxycorticosterone does not increase the excretion of potassium to nearly the levels attained by the infusion of moderate amounts of potassium salts[59] and the repeated administration of potassium salts produces a capacity to excrete potassium rapidly which cannot be reproduced by the administration of a large amount of adrenal steroids.[59,131] The capacity to vary excretion widely and to secrete potassium in response to administered potassium is retained by the adrenalectomized dog maintained on a fixed dosage of desoxycorticosterone acetate.[132] Conditions associated with high rates of potassium excretion are, in general, those in which a high intracellular potassium concentration might be predicted[59,129] and this may well be the most important factor in regulating excretion under these circumstances.

The mechanism for excreting potassium unlike that for sodium, does not appear to be subject to extrarenal influences which decrease excretion; all those recognized operate in the opposite direction. This circumstance may account for the fact that potassium excretion frequently appears to be relatively non-specific and related to a necessity to excrete anion at a time when circumstances favor retention of sodium. The continued loss of potassium in certain postoperative patients,[122,124] in individuals with so-called renal acidosis,[133] in cardiacs and cirrhotics treated with mercurial diuretics[59,134] may be largely on this non-specific basis.

It has been recognized that patients and experimental animals depleted of potassium tend to become alkalotic[135–137] and conversely that the production of alkalosis leads to depletion of potassium.[136] A renal mechanism is apparently involved but the nature of the relationship is obscure. The urine may remain acid despite severe alkalosis in the presence of potassium depletion;[138] although no quantitative studies are available, presumably the excretion of an alkaline urine may lead to increased excretion of potassium. It is known that the administration of potassium salts leads to the excretion of an alkaline urine.[59,110,139] This may, however, be a relatively transitory phase[59] and large amounts of potassium may be excreted in a strongly acid urine. Some of the apparent anomalies in this situation as well as in the excretion of potassium in general might well be explained were it possible to obtain a more complete picture of the intracellular electrolyte composition.

EXCRETION OF CALCIUM AND MAGNESIUM

The analytic methods for the determination of calcium and magnesium are relatively difficult and time-consuming so that

there have been few studies of the renal processes involved in the excretion of the divalent cations. An additional complexity results from the formation of non-ultrafilterable, unionized complexes between calcium ions and plasma protein and, in all probability, between magnesium ions and plasma protein. The amounts of these ions filtered at the glomerulus cannot be simply estimated as the product of glomerular filtration rate and plasma cation concentration. It is apparent from what little information is available that both are extensively reabsorbed, under normal circumstances the amount excreted being only a small fraction of the filtered.[140–142] When the amount filtered is increased, both the amount reabsorbed and the amount excreted are increased, as is the case with most of the inorganic electrolytes. The clearance of magnesium uncorrected for protein-binding may be as much as one-half the rate of glomerular filtration[142,143] at plasma magnesium levels approaching the maximum tolerated. There is, at present, no evidence of tubular secretion of the divalent cations. The mechanism by which the rate of excretion is regulated is unknown.

COMMENT

It is apparent from the many uncertainties and conflicting opinions that have been presented that our knowledge of the mechanisms of electrolyte excretion, and particularly of the regulation of electrolyte excretion, is fragmentary at best. In concluding, it is well to emphasize the deficiences of the available technics of study. The clearance method has proved particularly useful in the study of the relationship between plasma concentration (or filtered load) and excretion in cases in which this relationship is relatively simple and in which there is presumably a single tubular process involved. However, we are able to measure only what goes in one end and what comes out the other; information as to what happens in between is entirely inferential. When the intermediate events are multiple, as is probably the case with the electrolytes considered here, the partition of work among them can be arrived at only indirectly and at the risk of unproven assumptions. In this respect the puncture studies of individual nephrons have been extremely useful but their scope is of necessity limited because of the immense technical difficulties and the conditions of study are perforce such as to modify renal function appreciably.

Perhaps the most important problem lies in the uncontrolled, unmeasured and probably often unrecognized variables. This difficulty will be familiar to anyone who has attempted to explain the apparent vagaries of sodium excretion under presumably constant conditions. In the face of these unsurmounted difficulties in the analysis of electrolyte excretion in the normal subject, it would seem as yet premature to attempt to assign responsibility for various clinical abnormalities to one or another of the discrete renal functions or to any one of the extrarenal regulators of electrolyte excretion.

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Clinico-pathologic Conference

Chronic Renal Disease Due to Congenital Anomaly*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, C. R. (No. 178813), a white school boy ten years of age, entered the St. Louis Children's Hospital for the first of five admissions on November 11, 1945, because of chills and fever. The family history, past history and systemic review were irrelevant. Seven months before entry the patient developed an upper respiratory tract infection, and subsequently a urinary tract infection. Large numbers of white blood cells were found in his urine and the patient was given sulfonamide therapy to which he responded satisfactorily. He was then well until two weeks before admission when he again developed chills, fever, dysuria and pyuria. He was taken to another hospital where cystoscopy was performed; his bladder was said to have been dilated. He was given sulfonamide chemotherapy with apparent good clinical response.

In the Children's Hospital, cystoscopy was repeated and retrograde pyelograms were also made. Left hydroureter and bilateral hydronephrosis were demonstrated, and the patient was discharged on November 12, 1945.

One month later he re-entered for further study. A congenital deformity of the urethral valves was found, and these valves were destroyed by cautery. Hydroureter was also noted on the right side although it was less pronounced than on the left. While in the hospital the patient developed another acute respiratory infection which had completely subsided at the time of discharge.

His third entry was occasioned by another urinary tract infection with which were associated difficulty in voiding and left flank pain. Physical examination was entirely negative. The bladder was found to be atonic and the other abnormalities previously noted were again seen. The urinary tract infection subsided with chemotherapy and the patient was discharged. During his hospital stay the highest blood pressure recorded was 138/100.

In November, 1948, two years after the third admission, the patient again entered the St. Louis Children's Hospital. In the interim he had been seen at another large medical center where a "transurethral resection" had been performed. No other details of the procedure were available. During this two-year period the pediatrician who saw him noted persistent elevation of blood pressure and transient rises in nonprotein nitrogen. The patient remained free, however, from urinary tract infection and felt quite well. He entered merely for observation.

At the time of physical examination his blood pressure was 170/110. The patient was slightly obese. The eyegrounds were normal, and examination of the heart revealed it to be within normal limits in all respects. The kidneys could not be palpated. No other abnormal physical findings were noted.

The laboratory findings were as follows: Blood count: red cells, 3,340,000; hemoglobin, 11.8 gm. per cent. Urinalysis:

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albumin, 2 plus; sugar, negative; sediment, occasional white blood cell and rare red blood cell. Blood chemistry: non-protein nitrogen, 68 mg. per cent; total proteins, 5.9 gm. per cent; CO_2 combining power, 24 mEq./L; phosphorus, 5.5 mg. per cent; calcium, 12.8 mg. per cent. Roentgenogram of the chest: negative. Electrocardiogram: diphasic T waves in lead III and elevated S-T segment in lead IV.

Cystoscopy was again performed. The bladder was found to be very large, and there was a medium contracture of the bladder neck with scar tissue about the trigone. Retrograde pyelography revealed marked dilatation of the right ureter and somewhat less dilatation of the left ureter. Hydronephrosis was marked on the right, minimal on the left. Most of the contracted bladder neck was resected and the patient made an uneventful recovery.

In the interval between his fourth and fifth admissions the patient felt quite well. He was seen frequently by his pediatrician who noted that the non-protein nitrogen level averaged about 60 mg. per cent; the patient's blood pressure, however, was usually not above 125/75. Several weeks before the fifth entry he began to complain of headache and vomited occasionally. Re-examination at this time revealed that the non-protein nitrogen had risen to 125 mg. per cent, and the systolic blood pressure to 160 mm. of mercury. The urine showed large amounts of albumin, but the patient was free of edema. He entered the Children's Hospital in May, 1949.

Physical examination at that time revealed the temperature to be 37°C., pulse 100, respiration 20 and blood pressure 135/90. The patient appeared well nourished and comfortable, but his complexion was sallow and his breath uremic. The physical examination was otherwise not remarkable.

Laboratory data were as follows: Blood count: red cells, 3,900,000; hemoglobin, 10.7 gm. Urinalysis: albumin, 2 plus; sugar, negative; sediment, many white cells and some casts. Roentgenogram of the chest: negative. Electrocardiogram: normal.

Shortly after admission cystoscopy was performed and the right ureter was catheterized. Roentgenograms revealed a moderate constriction at the ureteropelvic junction which was thought to be responsible for the demonstrable hydroureter and hydronephrosis. The right kidney area was explored and the kidney was found to be hydronephrotic; the cortex was very thin. The ureter was dilated and tortuous as it entered the kidney pelvis. About 1 inch below the ureteropelvic junction the ureter appeared normal in diameter. The stricture was apparently due to pressure of an anomalous artery which crossed the ureter at this point. A kidney biopsy was done at the lower pole and the ureter was severed below the constriction and inserted at the biopsy opening. The patient made an uneventful recovery from the operative procedure and was discharged from the hospital.

During the seven months following discharge he felt fatigued but otherwise not uncomfortable. The non-protein nitrogen level averaged 110 mg. per cent and the blood pressure 180/120. Three months before his first admission to the Barnes Hospital he developed anorexia, nausea and vomiting which became much more severe five days before hospitalization. Concomitantly he developed increasing dyspnea and later drowsiness, edema of the lower extremities and finally continual vomiting. He was admitted to the Barnes Hospital on December 2, 1949.

At the time of entry, physical examination revealed temperature to be 36.5°C., pulse 130, respiration 30 and blood pressure 180/140. The patient's complexion was sallow; he sat upright in bed breathing rapidly and was quite apprehensive. The fundi were poorly visualized. Examination of the upper respiratory tract was negative. Crepitant rales were heard at the base of the left lung. The heart was enlarged to the left mid-axillary line, and a questionable pericardial friction rub was heard. The liver edge was percussed 4 cm. below the

costal margin. The kidneys were not felt. No edema was noted.

Laboratory data were as follows: Blood count: red cells, 2,230,000; hemoglobin, 5.9 gm.; white cells, 11,800; differential count: stab forms, 3 per cent; segmented forms, 86 per cent; lymphocytes, 10 per cent; monocytes, 1 per cent. Urinalysis: Specific gravity, 1.010; albumin, 2 plus; sugar, negative; centrifuged sediment, occasional red cell and a few white cells. Stool examination: guaiac negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 178 mg. per cent; chlorides, 113 mEq./L.; CO_2 combining power, 17.6 mEq./L.; total proteins, 5.5 gm. per cent; albumin, 4.5 gm. per cent; globulin, 1.0 gm. per cent; calcium, 6.7 mg. per cent; phosphorus, 11.0 mg. per cent. Roentgenogram of the chest: The heart was markedly increased in size, and the vascular markings throughout both lung fields were fuzzy, suggesting pulmonary congestion. Electrocardiogram: Incomplete right bundle branch block.

The patient was sedated and 1,000 cc. of 5 per cent glucose in saline were given very slowly by the intravenous route. Just before infusion was completed the patient became extremely dyspneic; his respiratory rate rose to 48 and his pulse rate to 136. His neck veins were distended. Moist rales were heard throughout the lower two-thirds of both lung fields but he was not cyanotic. He was given 0.5 gm. of aminophyllin by rectal suppository and improved rapidly. During his hospital stay vomiting became less frequent and finally ceased completely. Because of the experience with the intravenous infusion it was decided not to give the patient a blood transfusion. The prothrombin time, which had been 16.5 per cent of normal at the time of entry, rose to 80 per cent after vitamin K therapy. During his hospital stay the patient was afebrile. At the time of discharge on December 12, 1949, his blood pressure was 180/105 and his non-protein nitrogen 193 mg. per cent.

Following discharge the patient's condition deteriorated rapidly. He had increasing nausea and vomiting, dyspnea and edema. On December 23, 1949, he was admitted for the last time.

At the time of entry physical examination revealed the temperature to be 37.5°C., pulse 120, respirations 40 and blood pressure 170/100. The patient appeared extremely ill. He was propped up in bed leaning forward and his respirations were short and rapid. The skin had a waxy pallor. Examination of the fundi revealed marked narrowing of the retinal arteries. No hemorrhages or exudates were seen and the discs were not elevated. The neck veins were distended. There was dullness to percussion over both lung bases, particularly on the right, and above the area of dullness moist inspiratory rales could be heard. A loud gallop rhythm was audible over the entire precordium and a faint friction rub was noted along the left sternal border. The liver edge was felt 6 cm. below the right costal margin. Scattered petechial spots were present over the legs and 3 to 4 plus pitting edema extended up to the knees. The neurologic examination was not abnormal.

Laboratory findings were as follows: Blood count: red cells, 2,050,000; hemoglobin, 5.6 gm. per cent; white cells, 17,750. Urinalysis: Specific gravity, 1.007; albumin, 4 plus; sugar, negative; sediment, many white blood cells. Blood chemistry: non-protein nitrogen, 177 mg. per cent; chlorides, 85 mEq./L.; CO_2 combining power, 13.9 mEq./L.; prothrombin time, 41.5 per cent of normal; calcium, 4.8 mg. per cent; phosphorus, 15.3 mg. per cent. Electrocardiogram: incomplete right bundle branch block.

The patient failed to respond to all measures instituted; he became comatose soon after entry and died quietly on December 25, 1949.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case illustrates the tragic course of a certain form of renal disease. When this young man was ten years of age, he developed an upper respiratory tract infection and soon after

signs of a urinary tract infection. Studies at this time indicated an anatomic abnormality in his genitourinary tract. Dr. Harford, do you think the occurrence of these two infections was coincidental or does the second relate to the first?

DR. CARL G. HARFORD: Your question is difficult to answer. Acute respiratory tract infections are extremely common, and it is conceivable that transient bacteremia associated with such an infection might give rise to a urinary tract infection. On the other hand, urinary tract infections are commonly due to gram-negative bacilli, usually coliform organisms, and as a rule these organisms are not responsible for acute respiratory tract infections.

DR. ALEXANDER: I believe it was widely held years ago that respiratory infections not uncommonly gave rise to urinary tract infections, but I presume that this postulate is not tenable.

DR. W. BARRY WOOD, JR.: The experimental evidence in regard to the pathogenesis of pyelonephritis is extremely interesting in this regard. If the ureter is blocked and bacteremia produced, the kidney on the blocked side becomes pyelonephritic. It would seem to me, therefore, that a patient who has obstruction on one or both sides of his urinary tract and who subsequently acquires a respiratory tract infection with transient bacteremia could conceivably develop pyelonephritis in this manner. On the other hand, as Dr. Harford points out, one would expect the infection to be due to organisms usually found in the respiratory tract and that usually is not true in pyelonephritis.

DR. ALEXANDER: Dr. Schroeder, I believe that Dr. John Spitznagel and you are studying this problem. Would you discuss your experiments?

DR. HENRY A. SCHROEDER: Our experience confirms the investigation which Dr. Wood described. We have been able to produce hydronephrosis and subsequently pyelonephritis in rats in the manner described. It is interesting to note, however, that some renal function must remain in order for chronic hydronephrosis to develop. The ureter must not be completely blocked.

DR. ALEXANDER: This patient's urinary tract infections were treated with sulfonamides. Do you consider that the treatment of choice at the present, Dr. Harford?

DR. HARFORD: I believe that the newer antibiotics which are now available are preferable to sulfonamides, and would recommend the use of aureomycin or possibly of chloromycetin or terramycin.

DR. ALEXANDER: What dose of aureomycin do you suggest?

DR. HARFORD: Usually 2 gm. a day are sufficient. The concentration of chemotherapeutic agents in the urine is much higher than is the concentration of the agent in the blood, and thus one may obtain very satisfactory therapeutic levels with moderate doses orally.

DR. WOOD: It should be pointed out that aureomycin differs from streptomycin in that it is more active in an acid medium; thus it finds more use in urinary tract infections than does streptomycin, which when given should be accompanied by sufficient alkali to raise the pH of the urine above 7.4.

DR. HARFORD: I do not wish to convey the impression that the urinary level of a given drug is the only factor of importance. In pyelonephritis the organisms are present within the kidney parenchyma and, therefore, adequate blood levels of a given antibiotic are essential.

DR. ALEXANDER: Dr. Cordonnier, do the urologists frequently use sulfonamides in the treatment of urinary tract infections?

DR. JUSTIN J. CORDONNIER: The sulfonamides have been used a great deal because they are easily available, inexpensive and quite satisfactory in the treatment of many urinary tract infections, particularly mild ones. Aureomycin has been more expensive, but we have found it to be far superior to the sulfonamides in so far as results are concerned. Further, it does not cause the untoward reactions with which the sulfonamides are identified. In contrast with streptomycin, for example, aureomycin is much superior because organisms do not develop resistance

to it nearly as readily as is the case with streptomycin. Most of the organisms which cause urinary tract infections rapidly become resistant to streptomycin. In using aureomycin we have found that 0.25 gm. every six hours is quite satisfactory in most instances.

DR. ALEXANDER: This patient was said to have had congenital urethral valves. I was not aware that such an anomaly existed.

DR. CORDONNIER: Actually you are correct; the so-called urethral valves really represent abnormal structure of the posterior urethra. Ninety per cent of all cases of this abnormality occur in males. When present, the "valves" obstruct the outflow of urine. They are very difficult to demonstrate cystoscopically; thus one urologist may describe them at the time of cystoscopy while a second one will be unable to do so. That experience has been noted repeatedly, particularly in small children. It is important to remember that in a child the field of vision is very limited when one performs cystoscopy and the findings are difficult to interpret. Another factor which may be of importance in cases such as this one is neurogenic dysfunction of the bladder and ureters. Although in this particular case the so-called urethral valves were apparently present, the patient did not do well despite satisfactory destruction of the valves by cautery. There may well, therefore, have been a neurogenic basis for the patient's difficulty, possibly producing relaxation of the musculature of the bladder wall and ureters.

DR. ALEXANDER: The patient developed hydronephrosis and hydroureter. Do you believe that they arose because of this possible neurogenic element?

DR. CORDONNIER: That is a difficult question to answer. The entire clinical picture here could have resulted from an obstructive lesion at the bladder neck. Bilateral hydronephrosis and a large atonic bladder are both consistent with such a lesion.

DR. ALEXANDER: When the patient was admitted to the Children's Hospital for the last time it was found that hydronephrosis was marked on the right and minimal on the left. His blood pressure had begun to rise but renal function apparently was still fairly normal. Dr. Schroeder, do you think that it is a tenable theory that one may have hypertension due to hydronephrosis in one kidney with the other being normal?

DR. SCHROEDER: Yes, I think that is possible. It is known experimentally that an increase in intrapelvic pressure reduces renal blood flow. If such a situation becomes chronic, there is diminution in the vascular supply of the kidney. Occasionally in adults hypertension is associated with unilateral renal disease, and if the diseased kidney is removed the hypertension may occasionally disappear. Usually when there is hydronephrosis there is secondary infection, and it is likely in this case that the hypertension was partly of renal origin.

Dr. Goldring believes that this situation is rare, that the kidneys cannot be implicated causally in the ordinary case of hypertension and that the coexistence of hypertension and unilateral renal disease is usually a chance occurrence of two diseases. Dr. Homer Smith* was able to find only forty-seven cases in the literature in which hypertension was relieved by removal of a diseased kidney. To these I could add two cases I have followed; both patients have normal blood pressures more than ten years after nephrectomy, and both had severe hypertension before it; one has recently gone through pregnancy uneventfully. On the other hand, when hypertension has been initiated by unilateral renal disease in a person of the proper predisposition, and has existed for a number of years, arteriolar sclerosis develops in the opposite kidney. Nephrectomy at this stage will probably not terminate the hypertension. The experimental evidence is clear on this point.

If one studies the incidence of hypertension in the population by decades, one finds practically none in the second decade. The incidence of hypertension then gradually rises until in the eighth decade about

* SMITH, H. W. Hypertension and urologic disease. *Am. J. Med.*, 4: 724, 1948.

50 per cent of the population is so affected. In determining the incidence of hypertension with renal insufficiency one finds about 98 per cent in the younger age group and an incidence down to 50 per cent in the eighth. On the other hand, the incidence of hypertension in renal diseases without renal insufficiency is about 40 per cent at all ages, suggesting that two factors are important—a constitutional one and a renal one.

DR. WOOD: Do you believe that the kidney destruction was mainly on the basis of an inflammatory process, or do you believe the renal vessels will show marked involvement.

DR. ALEXANDER: I believe both factors will be operating.

DR. WOOD: The fact that the eyegrounds were not particularly abnormal at any time suggests to me that the inflammatory element must have been very important.

DR. ALEXANDER: I would agree. Dr. Cordonnier, would you comment on the importance of the constriction of the ureter by the aberrant artery?

DR. CORDONNIER: It should be pointed out that if this boy had not had hydronephrosis the aberrant vessel probably would not have caused difficulty. As the ureter and pelvis became enlarged because of hydronephrosis the vessel produced constriction. It is important to remember that the pyelograms done in 1945 showed poor function bilaterally. In other words, even at that date he had irreparable kidney damage; thus, none of the procedures attempted could have been expected to achieve satisfactory results.

DR. ALEXANDER: At the time of the admission before his death, Dr. Massie, the patient received intravenous saline by slow drip. He had no edema at that time but he developed marked pulmonary congestion at the conclusion of the infusion. Would you comment on this event?

DR. EDWARD MASSIE: When the patient was admitted to this hospital he had been vomiting excessively for two weeks and was very dehydrated. We decided that because of the prolonged vomiting sodium chloride should be given slowly. I believe that the attack of pulmonary edema would have occurred whether he received saline or glucose.

Because of his resistance to therapy it was often extremely difficult to treat the patient by the methods we considered indicated; thus, for example, the attack of pulmonary edema was combated with rectal aminophyllin rather than by the intravenous route.

DR. ALEXANDER: His heart became progressively enlarged in the last month of life. Do you attribute this to the development of hypertensive cardiovascular disease, or do you believe that the patient will have only pericarditis?

DR. MASSIE: I believe there will be evidence of both.

DR. ALEXANDER: This patient was not given a blood transfusion. Dr. Moore, would you comment on this decision?

DR. CARL V. MOORE: Two reasons might well influence the decision to avoid transfusion in a patient such as this one. In the first place, the patient's renal function was very poor and were he to have a hemolytic reaction further renal damage might occur. Secondly, he had developed pulmonary edema as a result of a saline infusion, and it was probably thought that blood might have the same untoward effect.

DR. ALEXANDER: Would you make some general comments on the giving of blood transfusions to people with renal disease, particularly with moderate renal disease? Do you believe there is a considerable risk attached to the procedure?

DR. MOORE: Dr. Loge has been studying this problem. He has given blood transfusions to a number of patients with severe renal disease in order to study the survival of transfused cells, and none of these individuals has developed any serious difficulty as the result of transfusion. Of course, in these experimental studies all possible precautions were taken to prevent hemolytic reactions.

It should also be pointed out that such patients should receive concentrated red

cells in order that a minimal amount of fluid and salt be given.

DR. ALEXANDER: Dr. Goldman, would you comment on the terminal blood chemical findings?

DR. MELVIN L. GOLDMAN: The patient had serious nitrogen retention. In acidosis from renal failure the CO_2 combining power characteristically falls as does the calcium. The phosphorus level rises to very high values. It is difficult to say whether the low chloride recorded was due to renal loss alone for considerable amounts may have been lost in vomitus.

DR. GUSTAVE J. DAMMIN: With the CO_2 combining power and chloride values so low, would anyone speculate on the possibility of potassium deficiency in this patient? Three factors work toward potassium deficiency, anorexia, which limits potassium intake, vomiting and impaired renal conservation.

DR. ROBERT J. GLASER: On the other hand, some patients with nitrogen retention actually get high potassium levels rather than low potassium levels. Dr. Finch and his co-workers have demonstrated this point quite well.

DR. MASSIE: The electrocardiogram did not show evidence of hypokalemia.

DR. ALEXANDER: In summary, it seems clear that this patient had renal failure, probably based on a congenital abnormality in the genitourinary tract with obstruction, hydronephrosis and pyelonephritis.

PATHOLOGIC DISCUSSION

DR. WILLIAM T. SNODDY: Moderate edema of all subcutaneous tissues and a healed scar at the site of the right nephrostomy were noted by external examination. All the serous cavities contained clear, light yellow fluid: 400 cc. were in the peritoneal cavity, and 700 cc. and 600 cc. in the right and left pleural cavities, respectively. In the pericardial sac there was a slightly increased amount of similar fluid and patches of fibrin on the epicardium. The heart was dilated and hypertrophied to 450 gm. without the presence of any intrinsic lesions. The lungs were heavy, congested and very moist with edema fluid. There was a moderate congestion in the liver and spleen.

The urinary bladder was dilated and the wall hypertrophied, but the urine which distended the organ could be easily expressed through the urethra with manual pressure. On opening the urethra scars in the superior prostatic portion were exposed. These scars extended laterally and superiorly from the verumontanum as irregular ridges which formed a wedge with the base in the lower portion of the trigone. The ureteral orifices were patent. The right ureter was dilated to a diameter of about 1 cm. and was tortuous so that folds of mucosa formed pseudovalves in the lumen. At the site of the surgical revision of the right ureteropelvic junction there were several prominent folds; but the lumen was easily patent to probing, as it was throughout the length of the ureter. The right renal pelvis and calyces were markedly dilated. The renal substance was reduced to a thin layer which was firmly adherent to the capsule. On the left the patent ureter and renal pelvis were only slightly dilated. The cortical surface of the left kidney was granular and pitted by large, flat-based scars. The cortex and medulla of this kidney were moderately reduced in thickness. No other significant lesions were present in other thoracic and abdominal viscera. Permission was not granted for examination of the neck organs or brain.

DR. DAMMIN: Grossly there was no remaining evidence of obstruction in the urinary tract, but the positions of the scars in the prostatic urethra correspond to those of one of the recognized types of congenital valves of the posterior urethra. Hugh Young* described three types of these valves: type I having leaflets arising from the distal portion of the verumontanum and extending inferiorly and laterally, type II having leaflets extending superiorly and

* YOUNG, H. H. Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases. Baltimore, 1937. Williams & Wilkins Co.

laterally from the proximal portion of the verumontanum and type III consisting of an iris diaphragm across the lumen of the urethra. Variants of the type I valve may have unilateral leaflets or bilateral separated or fused leaflets, and the diaphragm in the type III valve may be either proximal or distal to the verumontanum. The configuration of the scars in this case suggest a type II valve was present before the corrective operations.

Cases are also illustrated in Young's monograph which demonstrate the usual sequence of changes following this type of urethral obstruction. There is marked dilatation of all proximal portions of the urinary tract, hypertrophy of the walls of the urinary bladder and ureters and almost inevitably pyelonephritis in the hydronephrotic kidneys. It is interesting that not only these features are similar to those of the present case, but also that in two of Young's cases operations were performed with reduction of the valves to scarred ridges without preventing the progression of the lesions to fatal terminations. It is stated by Young that many cases might be diagnosed congenital hydroureter and hydronephrosis if these anomalies are overlooked. However, it is possible that too much importance has sometimes been attributed to these folds; the exact part they take in the production of obstruction of the urinary tract is often difficult to assess.

Figure 1 illustrates a section through the entire thickness of the right kidney. There is extensive destruction of renal substance in both the medulla and cortex with obliteration of the usual histologic markings. The pelvis is surrounded by fibrous tissue and the metaplastic epithelium is interrupted by foci of chronic inflammation. A more detailed view in Figure 2 shows the intensive interstitial fibrosis, interstitial infiltration of round cells, fibrosed glomeruli and dilated tubules which resulted from advanced pyelonephritis. There was no question that a marked loss of functioning renal substance had occurred. Very few nephrons of normal configuration could be identified in any of the sections. In sections of the left kidney (Figs. 3 and 4) changes essentially similar to those on the right are apparent with the additional finding of obvious thickening of the smaller arteries. The character of some of those vessels is shown in Figure 5, taken from a section especially stained to demonstrate elastic tissue. There are markedly thickened, sometimes discontinuous, internal elastic membranes, lumens of reduced diameter and thickened fibrous intimas.

One cannot say just how the vascular lesions in the kidneys were related to the patient's hypertension, for the ubiquitous presence of inflammation in these organs was sufficient cause for the changes in the vascular walls. On the other hand, the gross observations of the enlarged heart and the congestion of the viscera constitute evidence of prolonged hypertension ending in congestive failure. The lungs were grossly very edematous and sections as illustrated in Figure 6 show large amounts of precipitated protein in the alveoli and dilated capillaries filled with blood cells. There were also scattered small foci in sections of the heart in which a few myocardial fibers had lost their striations, were partially necrotic, and were surrounded by mononuclear cells. These changes were similar to those that occur with deficiency of potassium as has been observed in experimental animals and in a few reported human cases.* It hardly seems likely such minimal lesions in the myocardium could contribute mechanically to the development of cardiac failure, but they are at least consistent with the deficiency of potassium which may develop with chronic renal insufficiency as has been described in the recent literature.†

* Goodof, I. I. and MacBryde, C. M. Heart failure in Addison's disease with myocardial changes of potassium deficiency. *J. Clin. Endocrinol.*, 4: 30, 1944. Perkins, J. G., Petersen, A. B. and Riley, J. A. Renal and cardiac lesions in potassium deficiency due to chronic diarrhea. *Am. J. Med.*, 8: 115, 1950.

† Danowski, T. S. Newer concepts of the role of potassium in disease. *Am. J. Med.*, 7: 525, 1949. Tarail, R. and Elkinton, J. R. Potassium deficiency and the role of the kidney in its production. *J. Clin. Investigation*, 27: 557, 1948, and 28: 99, 1949.

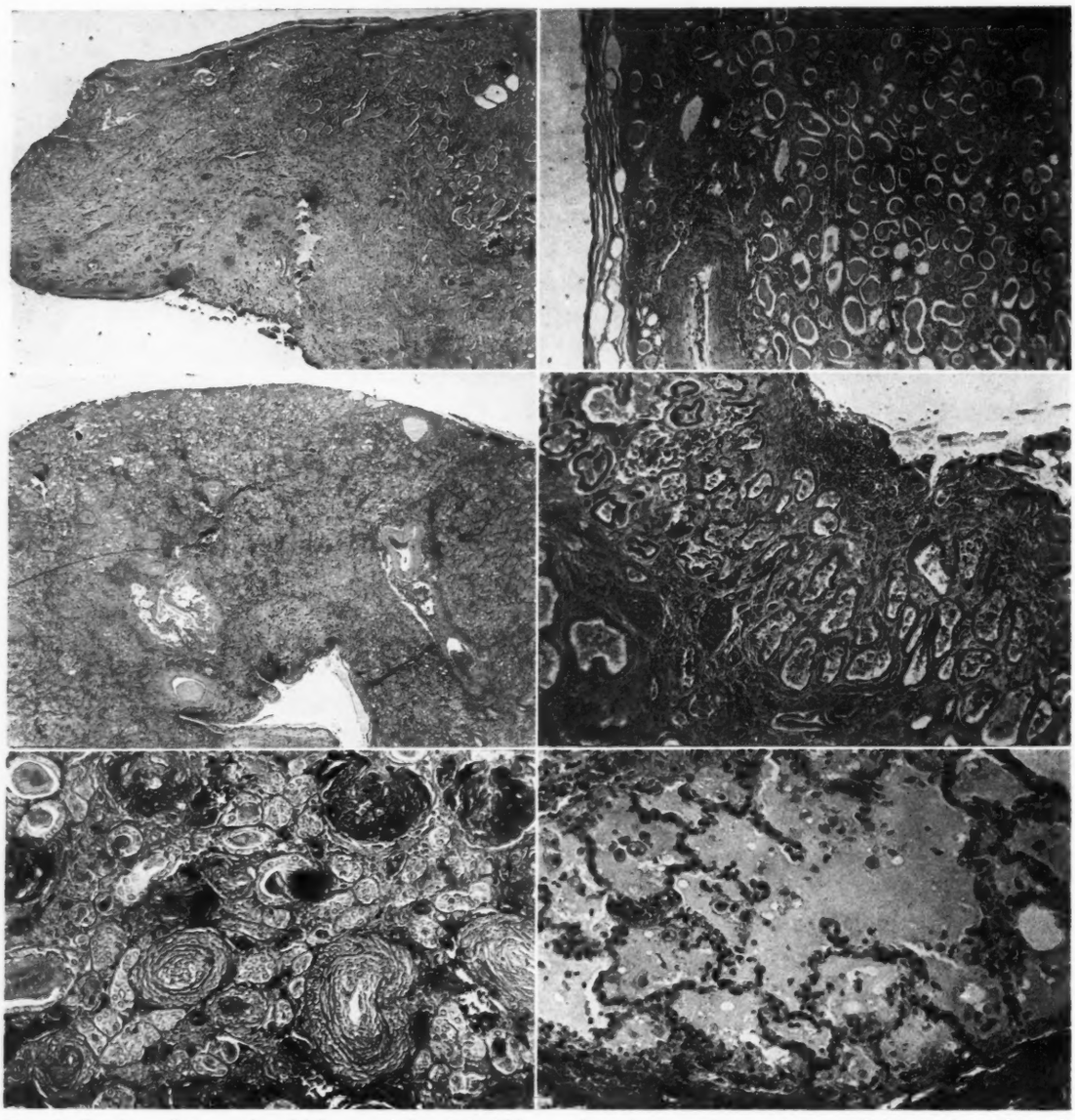


FIG. 1. Section of the entire thickness of the right kidney; there is extensive scarring and destruction of renal substance as well as foci of inflammation near the pelvis.

FIG. 2. The cortex of the right kidney in which chronic pyelonephritis has produced dilatation of the tubules which are filled with casts, interstitial fibrosis and inflammation, and destruction of the glomeruli.

FIG. 3. Section of the entire thickness of the left kidney at one of its thinnest points; thickened small arteries can be discerned even at this low magnification.

FIG. 4. The cortex of the left kidney with dilated tubules, interstitial inflammation and destruction of renal parenchyma resulting from hydronephrosis with superimposed pyelonephritis similar to that in the right kidney.

FIG. 5. Sclerotic and thickened small arteries in the cortex of the left kidney; Verhoeff-Van Gieson stain for elastic tissue.

FIG. 6. Dense deposits of precipitated protein in the alveoli and congested capillaries in the alveolar walls indicative of severe congestion and edema of the lungs; microscopic sections showed no evidence of bronchopneumonia.

In sections of the bone marrow there was evidence of increased activity of osteoclasts and a very slight amount of fibrosis in the marrow; these observations suggest slight overactivity of the parathyroids. Hypertrophy of the parathyroids was, of course, to be expected in this case of severe chronic renal disease, but those glands unfortunately could not be examined.

Combining the evidence from the clinical history and anatomic findings in this case the development of lesions probably followed the sequence of: (1) congenital valve of the urethra, (2) obstruction and dilatation of the urinary bladder and upper urinary tract, (3) superimposed pyelonephritis and (4) extreme destruction of renal tissue. Late in the course there was the development of hypertension and severe renal insufficiency with loss of potassium and overactivity of the parathyroids. Unfortunately, it is difficult to say how frequently or at what time hypertension occurs in many of the recorded cases of this type of urethral obstruction for they have, of necessity, been studied in children and the blood pressures are often not recorded.

Anatomic Diagnoses: (1) Scars of the posterior urethra at site of a removed congenital valve; (2) hypertrophy and dilatation of the urinary bladder with chronic cystitis; (3) hydroureter and hydronephrosis, right advanced, left moderate; (4) chronic pyelonephritis, bilateral, advanced; (5) hypertrophy and dilatation of the heart; (6) fibrinous pericarditis; (7) focal microscopic necroses in the myocardium; (8) congestion and edema of the viscera.

Acknowledgment: The photographs were made by the Department of Illustration, Washington University School of Medicine, St. Louis, Mo.

Book Review

The Child in Health and Disease. Clifford R. Grulee, M.D. and R. Cannon Eley, M.D., Editors. 1066 pages. Baltimore, 1948. The Williams & Wilkins Company. *Price* $12.00.

This recently published textbook of pediatrics is offered as a somewhat different approach to pediatric teaching in that it places the emphasis more on the concrete aspects of handling children in practice than on diagnosis and theory alone. This concept is indeed a useful one; hence, it is unfortunate that the circumstance of an intervening war should have made parts of the book already outmoded at the time of publication.

The list of contributors, a total of seventy-five, includes many outstanding names in United States pediatrics. The articles are well written, informative and, for the most part, practical. Useful charts for the evaluation of growth and development have been included.

Certain much needed innovations in a pediatric textbook have been introduced. Outstanding among these is the inclusion of an excellent section on adolescence, which in the past has been a no-man's-land between pediatrics and internal medicine. In this section is included a discussion of the gynecologic problems of adolescence. Another excellent feature is the inclusion of more than the usual space to some of the specialties such as diseases of the eye and of the whole respiratory tract.

From the strictly practical point of view it is gratifying to see chapters on "Accidental Poisonings of Infants and Children," on "First Aid in Pediatrics" and on "Pediatric Techniques." All these should prove very useful to a student or practicing physician and are not easily found in other standard texts.

The book has some serious defects, one of which is the fact already mentioned that some of the material is no longer current. Some articles contain very recent information as for example the inclusion of chloromycetin as a possible agent for the treatment of rickettsial diseases. On the other hand, in the discussion of histoplasmosis, which has recently assumed considerable importance in pediatrics, no reference is made to any work beyond 1942.

A second weakness is the fact that reference material is not always available. Many chapters are well documented whereas other important ones, such as the one on nutritional disturbances, have no bibliography at all. This variability from article to article is also apparent in the method of presentation of material. The format itself varies from section to section. Headings which appear as capitals in one part are put in italics elsewhere. References, when included, may appear either as footnotes or at the end of the chapter.

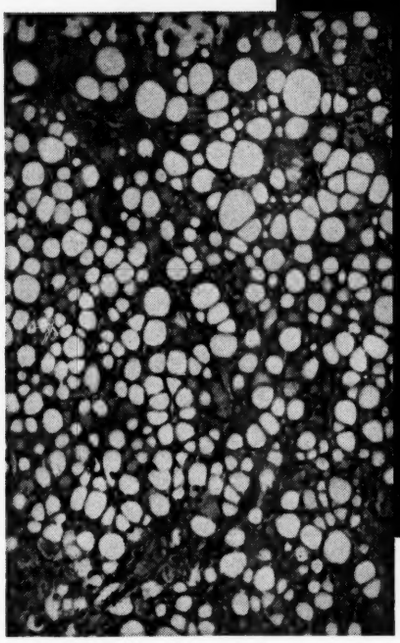
The factual content of the book, as said before, is generally well presented. There is, however, some duplication where different authors have apparently unwittingly covered the same subject without cross reference or addition. An example of this is the discussion of tuberous sclerosis and myasthenia gravis both in the chapter on organic diseases of the nervous system and the one on diseases of muscle. There are also some omissions. For a book meant to be largely practical, it is disappointing that some space has not been devoted to the handling of such common but not severe problems as mild diarrhea or simple croup. Again, some of the less common but nevertheless important diseases of childhood such as rheumatoid arthritis, periarteritis nodosa and disseminated lupus erythematosus have either been omitted or given very brief mention.

In concept this book offers much that is not to be found in the currently available texts. However, in execution some of the material is already outmoded and it is not so organized and written as to make it a convenient reference book for student or practitioner.

C. R.

CHOLINE LIPOTROPIC ACTION

IN THE PREVENTION AND REVERSAL OF FATTY INFILTRATION



PATIENT . . . Middle aged female, with history and findings suggesting cirrhosis: loss of appetite, nausea, vomiting, vague gastrointestinal complaints, enlarged liver. Liver biopsy showed extensive fatty changes without fibrosis, indicating that the condition would be still amenable to treatment.

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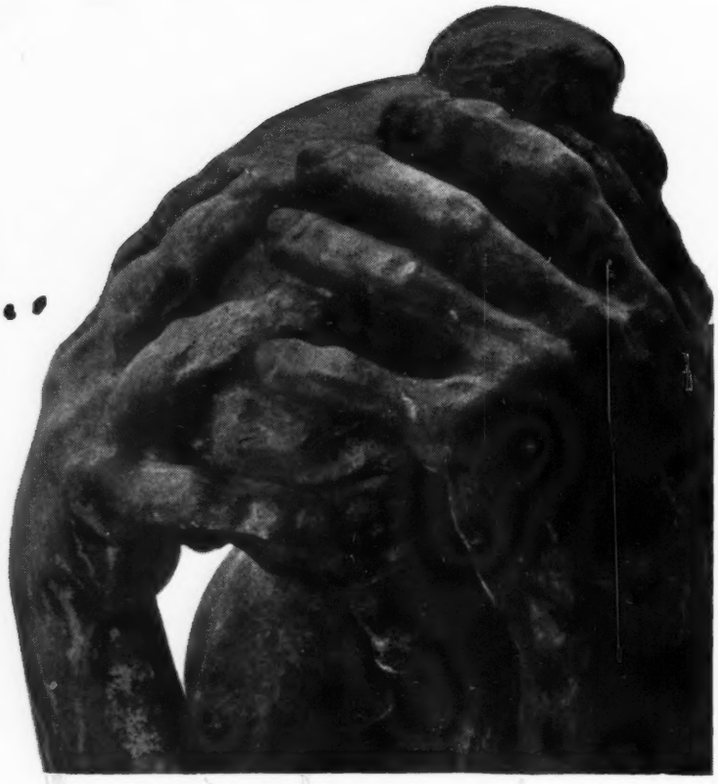

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1. Dieckmann, W. J., and Priddle, H. D.: Am. J. Obstet. & Gynec. *57*:541, 1949
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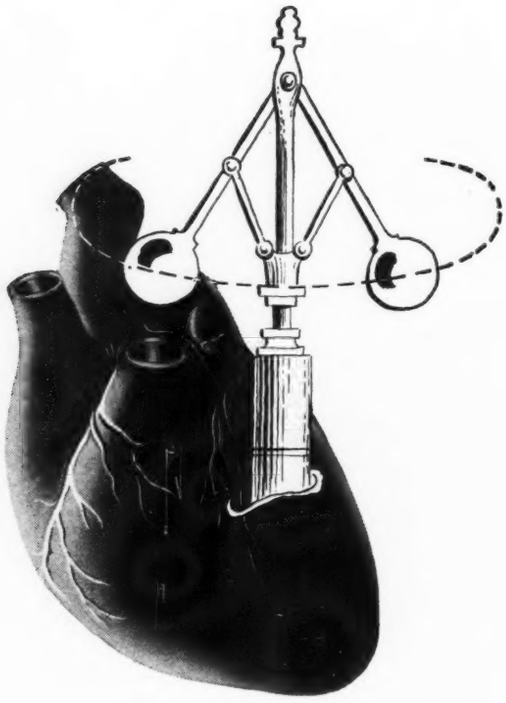

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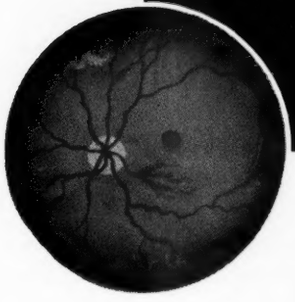
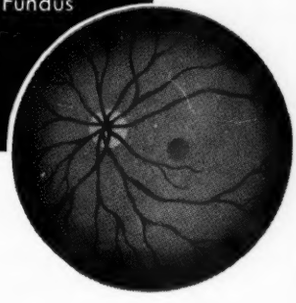
Ocular Fundus in Degenerative Vascular Disease—Hypertension, Diabetes, Arteriosclerosis—note tortuous blood vessels, areas of exudation, hemorrhagic areas.



Normal Ocular Fundus



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*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.

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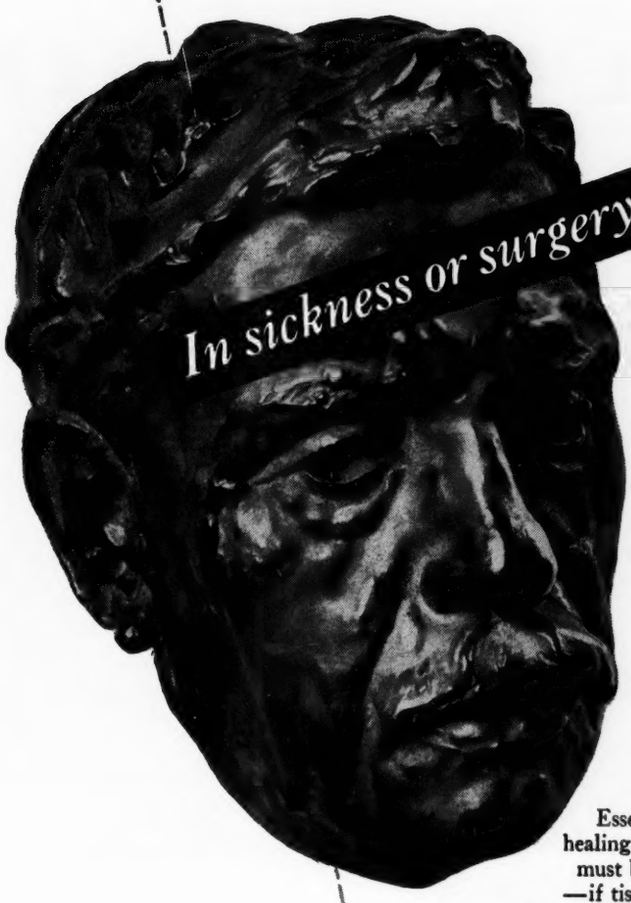

In sickness or surgery, play safer with . . .

"Saturation Dosage"

of vitamins b *and* c

Depletion of the critical water-soluble B complex and C vitamins occurs so commonly in the presence of physical pathology, as to make a presumption of nutritive impairment[2] almost axiomatic. Essential to normal cell metabolism and wound healing, these poorly-stored, readily-diffusible factors must be replenished — usually by *massive dosage* —if tissue rehabilitation[3] and return to health[4] are to be expedited. • Allbee with C 'Robins' provides this all-important "saturation dosage" in convenient capsule form. It incorporates the important B factors in 2 to 15 times daily requirements, plus 250 mg. of vitamin C — *the highest strength of ascorbic acid available today in a multi-vitamin capsule.* • Its prescription represents a sound contribution toward decisive recovery from disease, or toward pre- and post-operative nutritional support.[1]

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Ascorbic acid (C)	250 mg.

REFERENCES: 1. Coller, F. A. and DeWeese, M. S.: Preoperative and Postoperative Care, J.A.M.A., 141:641, 1949. 2. Jolliffe, N. and Smith, J. J.: Med. Clin. North America, 27:567, 1943. 3. Kruse, H. D.: Proc. Conf. Convalescent Care, New York Acad. Med., 1940. 4. Spies, T. D.: Med. Clin. North America, 27:273, 1943.

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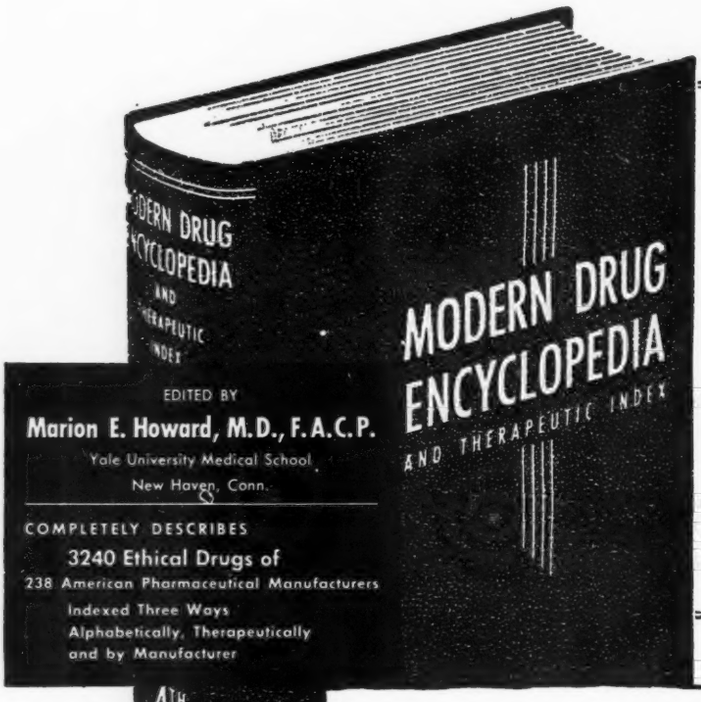

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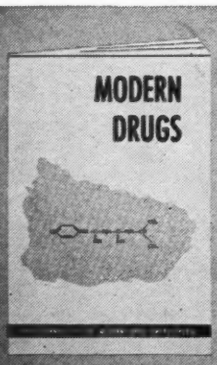

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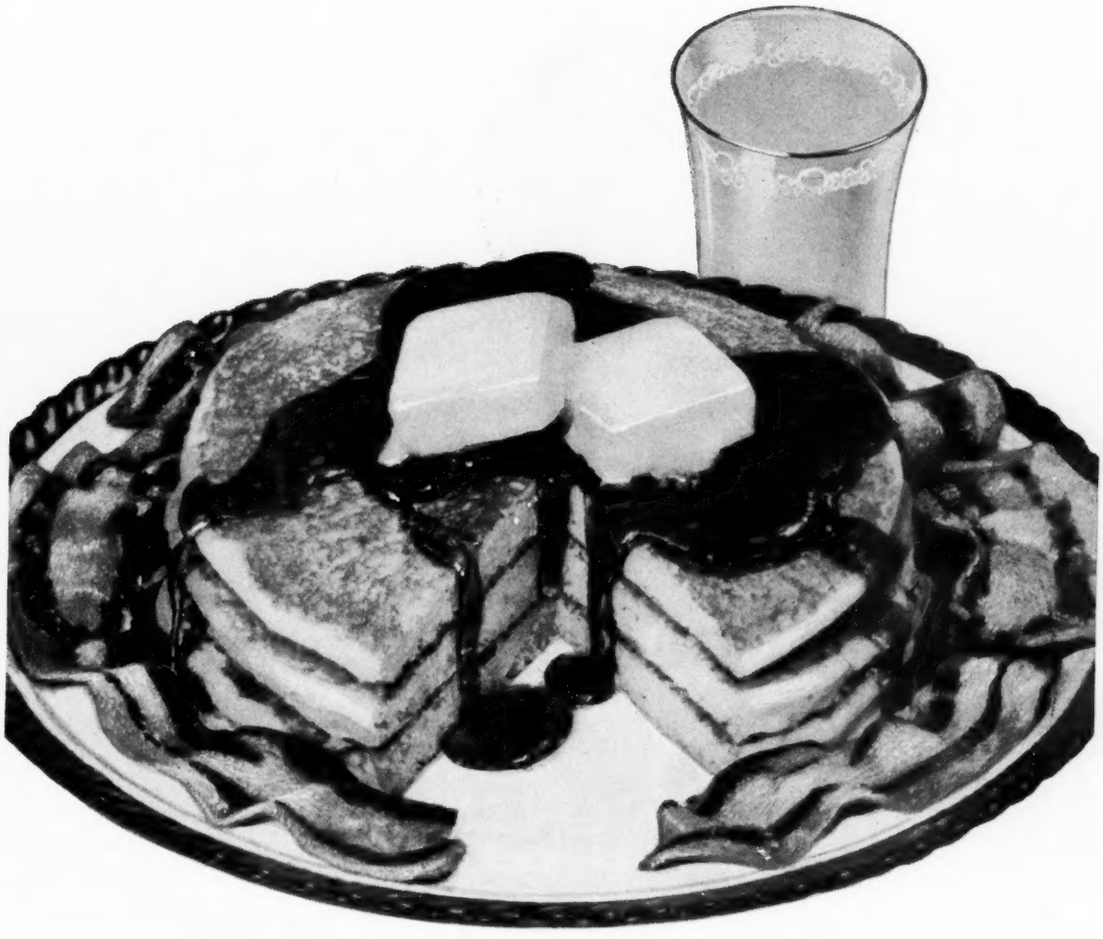

A Real American Breakfast

That a nutritious breakfast providing generous amounts of high quality protein prevents late morning hypoglycemia has been amply demonstrated. As shown by Thorn and co-workers,[1] and later confirmed by Orent-Keiles,[2] ". . . breakfast high in protein and low in fat and carbohydrate was followed by an improved sense of well-being and no symptoms of hypoglycemia."

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The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

(1) Thorn, G.W.; Quinby, J.T., and Marshall, C., Jr., Ann. Int. Med. 18:913 (June) 1943.
(2) Orent-Keiles, E., and Hallman, L. F., Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

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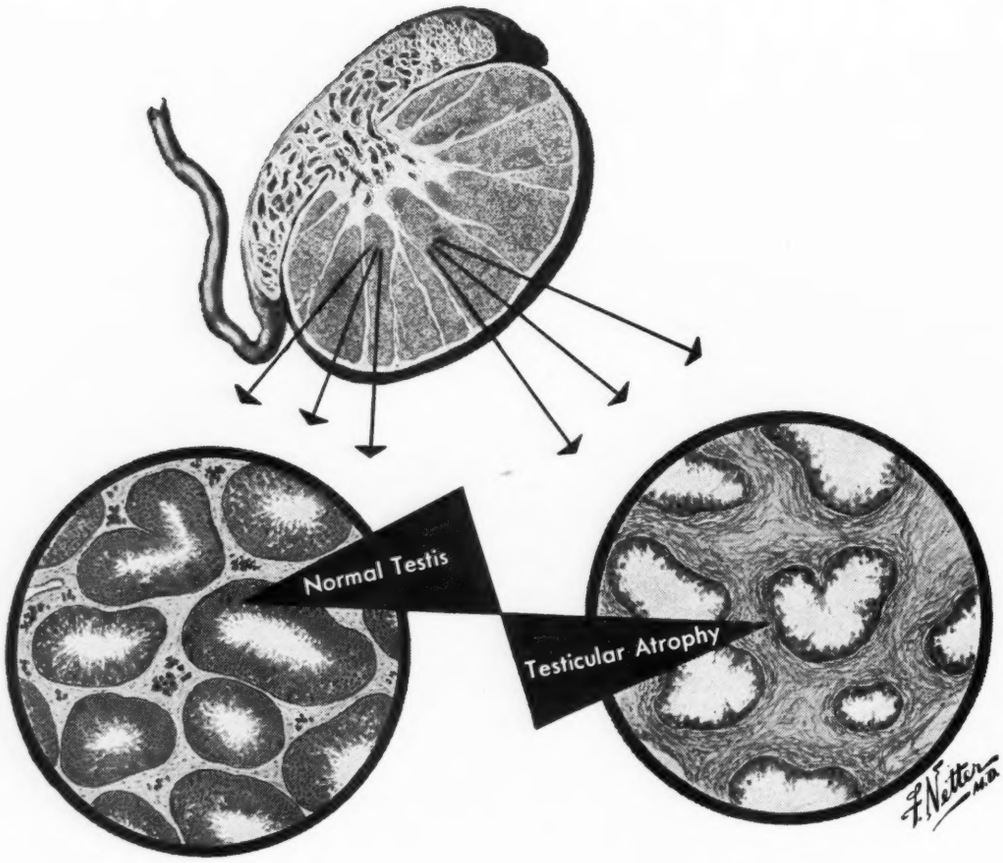

Testicular Atrophy!

Bilateral testicular atrophy occurring before puberty usually leads to primary hypogonadism or eunuchoidism. The cause of atrophy in early life is usually an orchitis of some type such as that occurring after mumps. *Much* more common, however, is testicular functional failure which may occur at any age after puberty and be associated with the climateric syndrome.

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Testosterone Propionate Armour . . . (for injection) 25 milligrams per c.c.—in packages of 6-1 c.c. ampules, 50-1 c.c. ampules, 1-10 c.c. vial.

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Most effective [1,2] and well tolerated [3,4] White's Mol-Iron Liquid also has real taste-appeal for your patients. Children especially, even those who are medicine-shy, will readily follow your dosage schedule when you prescribe good-tasting White's Mol-Iron Liquid.

Each delicious teaspoonful of Mol-Iron Liquid contains 40 mg. of elemental iron.

May be conveniently administered in a small quantity of water or fruit juice, club soda or ginger ale (not in milk).

Recommended Therapeutic Dosage:

CHILDREN: Up to 2 years—½ teaspoonful 3 times daily
2 to 6 years—1 teaspoonful twice daily
6 to 12 years—1 teaspoonful 3 times daily
ADULTS: 2 teaspoonfuls 3 times daily

Supplied: Bottles of 12 fluid ounces.

ALSO AVAILABLE: —Mol-Iron Tablets—bottles of 100 and 1000.
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1. Dieckmann, W. J., and Priddle, H. D.: Am. J. Obst. & Gynec. *57*:541 (1949).
2. Chesley, R. R., and Annitto, J. E.: Bull. Margaret Hague Mat. Hosp. *1*:68 (1948).
3. Neary, E. R.: Am. J. M. Sc. *212*:76 (1946).
4. Kelly, H. T.: Pennsylvania M. J. *51*:999 (1948).

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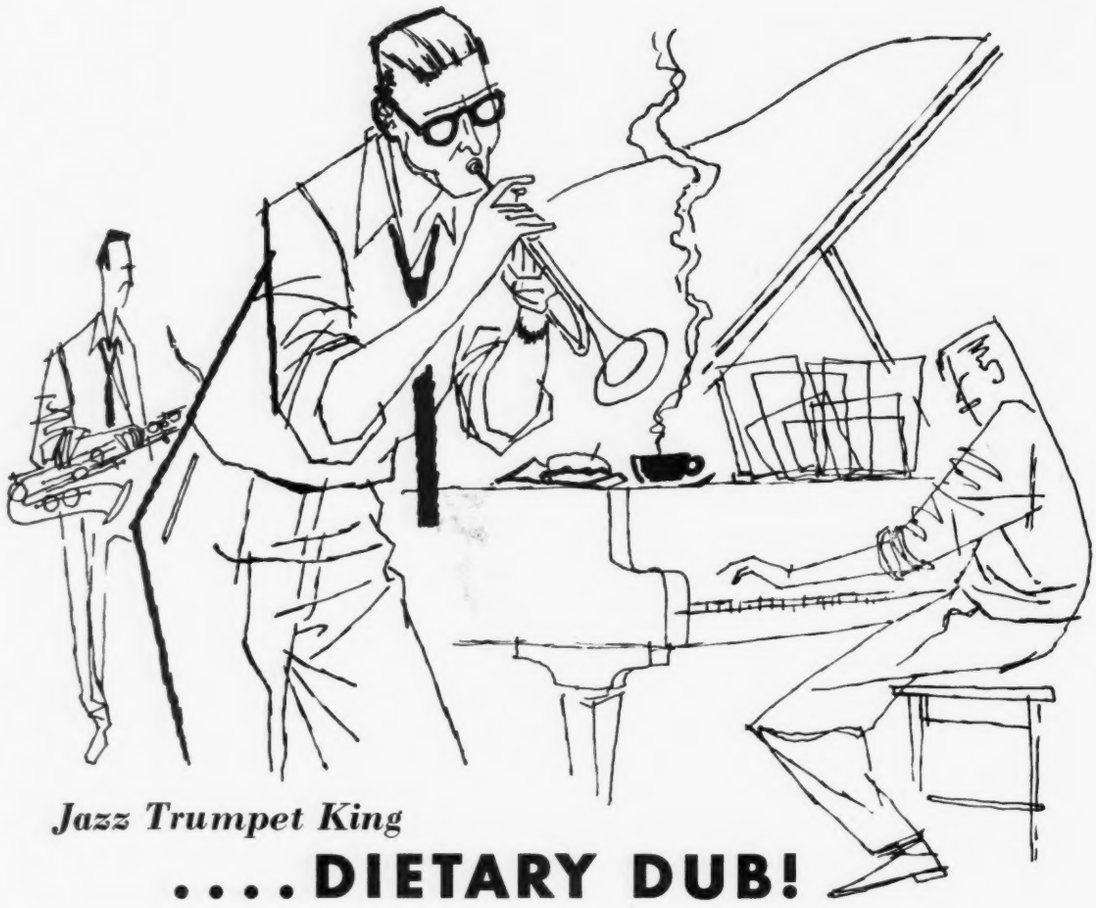

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● His is a life of big name bands and one night stands—of hamburgers with and coffee without. Instrumental balance is one thing, nutritional balance another. So eventually he winds up playing second fiddle to a subclinical vitamin deficiency and comes to you for advice. Because multiple B complex deficiencies are common in such cases, you might logically supplement a corrected diet with SUR-BEX, a stable vitamin product that supplies therapeutic amounts of five B vitamins—plus liver fraction and brewer's yeast for added B factors. They're triple coated to *seal in* the odor. When ascorbic acid is also needed, prescribe SUR-BEX WITH VITAMIN C tablets. These capsule-shaped tablets supply 150 mg. of ascorbic acid in addition to the B factors present in SUR-BEX. Both are available at pharmacies in bottles of 100, 500 and 1000 tablets.

Abbott

NOTE THE FORMULA

Each Sur-bex Tablet Contains:

Thiamine hydrochloride	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid (as calcium pantothenate)	10 mg.
Liver fraction 2, N.F.	0.3 Gm. (5 grs.)
Brewer's yeast dried	0.15 Gm. (2½ grs.)

Sur-bex with Vitamin C contains 150 mg. of ascorbic acid in addition to the vitamin B complex factors.

SPECIFY: **Sur-bex®**

(Abbott's Vitamin B Complex Tablets)

Advertising Index

October 1950

NEW!

Carmethose-Trasentine

Doubly effective in relieving gastric discomfort...

Carmethose-Trasentine is a logical combination of a new *antacid* and an effective *antispasmodic* to control gastric discomfort.

Controls hyperacidity... This combination lowers gastric acidity and forms a protective coating which has been observed in the stomach for as long as three hours.

Controls spasm... Carmethose-Trasentine relieves gastric pain also by relaxing smooth muscle spasm. The anesthetic effect of Trasentine further controls gastric irritability. Carmethose-Trasentine is non-constipating, palatable and eliminates acid-rebound.

Issued: Carmethose-Trasentine Tablets: sodium carboxymethylcellulose, 225 mg.; magnesium oxide, 75 mg.; Trasentine, 25 mg. Bottles of 100.

Carmethose without Trasentine is also available for use in cases where the antispasmodic component is considered unnecessary. Available as Tablets, each containing sodium carboxymethylcellulose 225 mg., with magnesium oxide 75 mg., and as Liquid, a 5% solution of sodium carboxymethylcellulose.

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